Consommation et Affaires commerciales Canada
Bureau des brevets
Ottawa, Canada
K1A 0C9

Consumer and Corporate Affairs Canada
Patent Office

(21) (A1) 2,092,852
(22) 1993/03/29
(43) 1993/10/02

5,066,1/41

(51) INTL.CL.[5] C07D-233/54; C07D-401/12; C07D-403/02; C07D-405/00; C07D-417/00; A61K-031/415; A61K-031/44; A61K-031/495; A61K-031/535

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Imidazole Derivatives, Their Method of Preparation and Their Application in Therapeutic

(72) Dodey, Pierre - France ;
Bondoux, Michel - France ;
Renaut, Patrice - France ;
Pruneau, Patrice - France ;

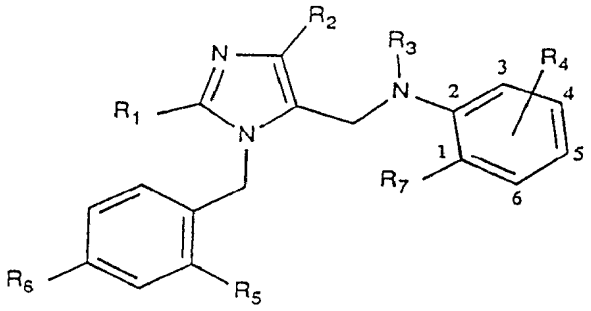
(71) Same as inventor

(30) (FR) 92 03 944 1992/04/01

(57) 11 Claims

ABSTRACT OF THE DISCLOSURE

The present invention relates to the phenylaminomethylimidazoles of the formula



(I)

(in which the groups R_1 to R_7 are defined as indicated in the description).

It further relates to their method of preparation and to their application in therapeutics as angiotensin II antagonists, which are useful in the treatment of hypertension, circulatory disorders and glaucoma.

Imidazole derivatives, their method of preparation and their application in therapeutics

The present invention relates to imidazole derivatives, to their method of preparation and to their application in therapeutics as agents useful in the treatment of hypertension, circulatory disorders and glaucoma.

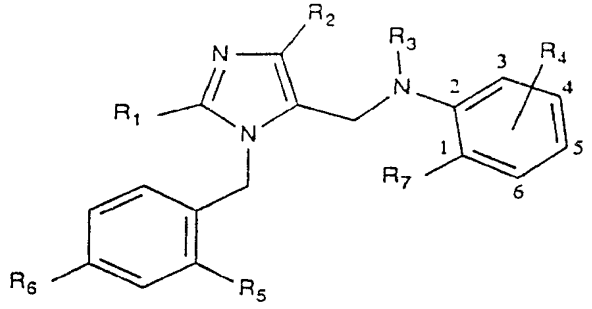
A number of imidazole derivatives are already known which are angiotensin II inhibitors useful as antihypertensives.

Patent applications EP-A-403 158 and EP-A-403 159 describe imidazolylalkenoic acids carrying an unsaturated chain in the 5-position of the imidazole ring. Patent application EP-A-465 368 describes sulfur-containing imidazole derivatives. Patent application WO-A-91/00277 describes substituted imidazoles carrying an aldehyde group in the 5-position of the imidazole ring. Patent application EP-A-427 463 describes substituted N-(imidazolyl)alkylalanine derivatives carrying an amino acid in the 5-position of the imidazole ring. Patent application EP-A-324 377 describes imidazole derivatives which are recommended as diuretics, antiinflammatories and antihypertensives. Patent application EP-A-253 310 describes imidazole derivatives carrying a hydroxymethyl substituent in the 5-position of the imidazole ring.

None of these documents of the prior art describes or suggests imidazole derivatives carrying a phenylaminomethyl substituent in the 5-position of the imidazole ring.

The present invention therefore proposes imidazole derivatives carrying a phenylaminomethyl substituent in the 5-position of the imidazole ring.

The compounds according to the invention are selected from the group consisting of:
(i) the phenylaminomethylimidazoles of the formula

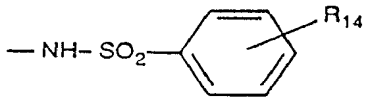


(I)

in which:
- R_1 is a C_1-C_4-alkyl group;
- R_2 is the hydrogen atom, a halogen, a C_1-C_4-alkylthio group or a C_1-C_3-perfluoroalkyl group;
- R_3 is the hydrogen atom, a C_1-C_4-alkyl group or a group COR_8, in which R_8 is a C_1-C_4-alkyl group;
- R_4 is in the 3-, 4-, 5- or 6-position and is the hydrogen atom, one or more C_1-C_4-alkyl, C_1-C_4-alkoxy, azido or nitro groups or one or more halogens, or forms a 2-aminonaphthyl group with the aminophenyl group to which it is bonded;
- R_5 is a hydrogen atom or a halogen;
- R_6 and R_7, which are identical or different, are each a tetrazol-5-yl group or a group COR_9, in which R_9 is:
  - a hydroxyl group,
  - a C_1-C_{16}-alkoxy group,
  - a cyclopropylmethoxy group,
  - a phenoxy group,
  - a benzyloxy group,
  - a 2-phenylethoxy group,
  - a glyceryl group,
  - an isopropylideneglyceryl group,

- a 2-methoxyethoxy group,
- a 2-oxobutoxy group,
- a 1-methyl-2-oxobutoxy group,
- a 2-(N,N-diethylamino)ethoxy group,
- a morpholinoethoxy group,
- an N-(ethoxy)nicotinamide group,
- a group $O-CHR_{15}-O(CO)-R_{12}$, in which R_{15} is the hydrogen atom or a C_1-C_3-alkyl group and R_{12} is a C_1-C_7-alkyl group, a cyclopentyl group, a cyclohexyl group, a cyclopentylmethyl group or a cyclohexylmethyl group,
- an oxyacetate group of the formula $O-CHR_{17}-CO_2-R_{16}$, in which R_{16} and R_{17} are each independently the hydrogen atom or a C_1-C_5-alkyl group,
- an oxyacetamide group of the formula $O-CH_2-CO-NR_{10}R_{11}$, in which R_{10} and R_{11}, which are identical or different, are each a C_1-C_4-alkyl group or a hydroxyethyl group or form a 4-methylpiperazin-1-yl group with the nitrogen atom to which they are bonded, or
- an amino group of the formula $-NR_{18}R_{19}$, in which R_{18} and R_{19} are each independently the hydrogen atom, a C_1-C_4-alkyl group, a methoxy group or a 2-(N,N-dimethylamino)propyl group, or $-NR_{18}R_{19}$ is an amino acid residue of the glycine or valine structure in which the acid group is optionally protected in the form of an ester or amide;

- R_6 is also:
- a group COR_{13}, in which R_{13} is a methylsulfonylamino group of the formula $-NH-SO_2-CH_3$ or an arylsulfonylamino group of the formula



in which R_{14} is the hydrogen atom, a halogen, an azido group, a C_1-C_4-alkyl group or a methoxy group and can be located in the ortho-, meta- or para-position; and

- R_3 and R_7 taken together can form, with the nitrogen atom and the phenyl group to which they are respectively bonded, a 2-carboxyindol-1-yl or 2-ethoxycarbonylindol-1-yl ortho-fused nitrogen-containing heterocycle; and

(ii) the addition salts of the compounds of formula I with mineral and organic acids or with mineral and organic bases.

C_1-C_7-Alkyl group is understood here as meaning a linear, branched or cyclic alkyl group containing up to 7 carbon atoms. The preferred alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl and pentyl groups.

C_1-C_{16}-Alkoxy group is understood here as meaning a group in which the alkyl radical is linear, branched or cyclic and contains up to 16 carbon atoms. The preferred alkoxy groups are methoxy, ethoxy, pentoxy and cyclopropylmethoxy groups.

C_1-C_4-Alkylthio group is understood here as meaning a group in which the alkyl radical is linear or branched and contains up to 4 carbon atoms. The preferred alkylthio groups are methylthio and ethylthio groups.

Halogen is understood here as meaning the fluorine atom, the chlorine atom, the bromine atom or the iodine atom.

The preferred C_1-C_3-perfluoroalkyl groups will be trifluoromethyl and perfluoroethyl groups.

The preferred addition salts with mineral and organic acids will be the addition salts formed with hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, malic, acetic, glutamic, tartaric,

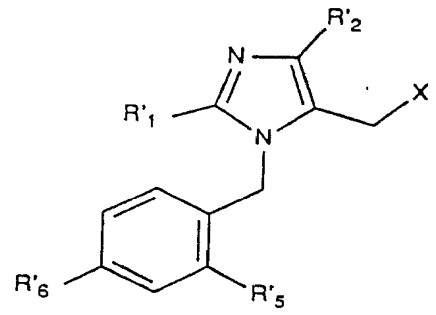
lactic, citric, aspartic, oleic, gluconic, ascorbic, valeric, succinic, ethylsuccinic, fumaric, oxalic, gallic, pivalic, capric, decanoic, heptanoic, propionic, caproic, stearic, isethionic, ethanedisulfonic, methanesulfonic, naphthalenesulfonic and metasulfobenzoic acids.

The preferred addition salts with mineral or organic bases will be the addition salts formed with sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, manganese hydroxide, lithium hydroxide, lysine, cysteine, arginine, monoethanolamine, meglumine, betaine, diethylamine and dicyclohexylamine.

The preferred compounds according to the invention are the compounds of formula I in which R_6 and R_7 are a sulfonylaminocarbonyl group or a group COOH, as well as their salts obtained by reaction with an organic or mineral base. The compounds of formula I salified by reaction with an organic or mineral acid will be particularly preferred.

The compounds of formula I according to the invention can be prepared by a method wherein:

(a) a compound of the formula



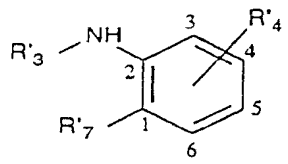
(II')

in which:

- R'_1 is a C_1-C_4-alkyl group;

- R'_2 is the hydrogen atom, a halogen, a C_1-C_4-alkylthio group or a C_1-C_3-perfluoroalkyl group;
- R'_5 is a hydrogen atom or a halogen;
- R'_6 is a cyano group or a group COR'_9, in which R'_9 is a C_1-C_{16}-alkoxy group, a benzyloxy group or an isopropylideneglyceryl group; and
- X is a halogen, especially the chlorine atom, or a paratoluenesulfonyl group,

is subjected to nucleophilic substitution by reaction with a compound of the formula



(III')

in which:

- R'_3 is the hydrogen atom or a C_1-C_4-alkyl group;
- R'_4 is in the 3-, 4-, 5- or 6-position and is the hydrogen atom, one or more C_1-C_4-alkyl, C_1-C_4-alkoxy, azido or nitro groups or one or more halogens, or forms a 2-aminonaphthyl group with the aminophenyl group to which it is bonded;
- R'_7 is ā cyano group or a group COR'_9, in which R'_9 is:

  - a C_1-C_{16}-alkoxy group, a benzyloxy group, an isopropylideneglyceryl group, a phenoxy group, a 2-phenylethoxy group, a 2-methoxyethoxy group, a 2-oxobutoxy group, a 1-methyl-2-oxobutoxy group or a 2-(N,N-diethylamino)ethoxy group,

  - a group $O-CHR_{15}-O(CO)-R_{12}$, in which R_{15} is the hydrogen atom or a C_1-C_3-alkyl group and R_{12} is a C_1-C_7-alkyl group, a cyclopentyl group, a cyclohexyl group, a cyclopentylmethyl group or a cyclohexylmethyl group,

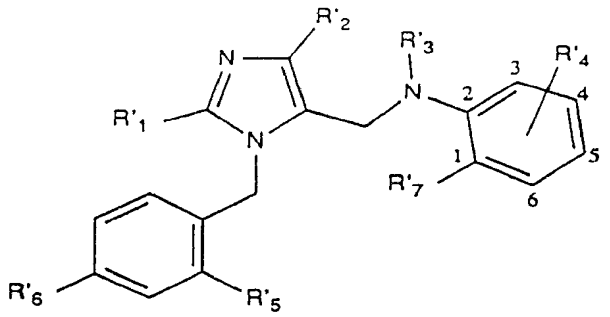
- an oxyacetate group of the formula $O-CHR_{17}-CO_2-R_{16}$, in which R_{16} and R_{17} are each independently the hydrogen atom or a C_1-C_5-alkyl group,

- an oxyacetamide group of the formula $O-CH_2-CO-NR_{10}R_{11}$, in which R_{10} and R_{11}, which are identical or different, are each a C_1-C_4-alkyl group or a hydroxyethyl group, or

- an amino group of the formula $-NR_{18}R_{19}$, in which R_{18} and R_{19} are each independently the hydrogen atom, a C_1-C_4-alkyl group, a methoxy group or a 2-(N,N-dimethylamino)propyl group, or $-NR_{18}R_{19}$ is an amino acid residue of the glycine or valine structure in which the acid group is optionally protected in the form of an ester or amide; and

- R'_3 and R'_7 taken together can form, with the nitrogen atom and the phenyl group to which they are respectively bonded, a 2-carboxyindol-1-yl or 2-ethoxycarbonylindol-1-yl ortho-fused nitrogen-containing heterocycle,

in an anhydrous medium, in the presence or absence of a polar or non-polar and aprotic solvent, for example toluene, xylenes, tetrahydrofuran, dimethylformamide, chlorinated hydrocarbons, ethers, dioxane, N-methylpyrrolidin-2-one, N,N'-dimethylpropyleneurea or dimethyl sulfoxide, and in the presence or absence of a strong base, for example triethylamine, 2,6-lutidine, sodium or potassium hydride, potassium or lithium hexamethyldisilylamide or lithium diisopropylamide, at a rate of 1 mol of compound II' to 1 to 20 mol of compound III', at a temperature between room temperature (15-25°C) and about 200°C, for 0.1 to 12 hours, to give a compound of the formula



(I')

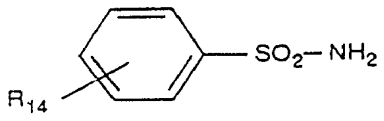
in which R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 are defined as indicated above; and

(b) if necessary, the resulting compounds of formula I' can be subjected to the following treatments:

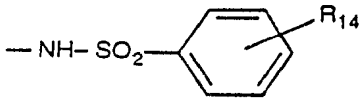
(i) the compounds of formula I' in which at least one of the groups R'_6 and R'_7 is a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group are saponified by the methods known to those skilled in the art, especially in the presence of a strong base, for example an aqueous solution of sodium or potassium hydroxide, in dimethoxyethane or an alcohol such as methanol, to give a compound of formula I in which R_6 and R_7 are a group COOH or R_6 is a group COOH and R_7 is a group COR_9 in which R_9 is a C_1-C_{16}-alkoxy group;

(ii) the compounds thus obtained in stage (i) are esterified by the methods known to those skilled in the art, especially by reaction with an appropriate alcohol or by reaction with an appropriate halogenated derivative, to give a compound of formula I in which R_6 and R_7 are a group COR_9 in which R_9 is as defined for the groups R'_9 indicated above;

(iii) methylsulfonamide or an arylsulfonamide of the formula



in which R_{14} is the hydrogen atom, a halogen, an azido group, a C_1-C_4-alkyl group or a methoxy group, is acylated with a monoacid obtained in stage (i) by the methods known to those skilled in the art, especially in the presence of a coupling reagent, for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or N,N-dicyclohexylcarbodiimide, to give a compound of formula I in which R_6 is a group COR_{13} in which R_{13} is a methylsulfonylamino group of the formula $-NH-SO_2-CH_3$ or an arylsulfonylamino group of the formula



in which R_{14} is defined as indicated above, R_7 is a group COR_9 in which R_9 is a C_1-C_{16}-alkoxy group, and R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for R'_1, R'_2, R'_3, R'_4 and R'_5 respectively;

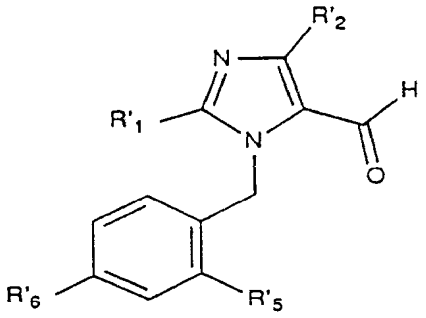
(iv) the compounds of formula I' in which R'_3 is the hydrogen atom and R'_1, R'_2, R'_4, R'_5, R'_6 and R'_7 are defined as indicated above are acylated by the methods known to those skilled in the art, especially by reaction with an acid anhydride, for example acetic anhydride, to give a compound of formula I in which R_3 is a group COR_8 in which R_8 is a C_1-C_4 alkyl group, and R_1, R_2, R_4, R_5, R_6 and R_7 are defined as indicated above for R'_1, R'_2, R'_4, R'_5, R'_6 and R'_7 respectively;

(v) if necessary, the compounds of formula I' in which at least one of the groups R'_6 and R'_7 is a group COR'_9

in which R'_9 is a C_1-C_4-alkoxy group, a benzyloxy group or an isopropylideneglyceryl group are deprotected by the methods known to those skilled in the art, especially by treatment in an acid medium or by catalytic hydrogenation, to give a compound of formula I in which at least one of the groups R_6 or R_7 is a group COOH or CO-glyceryl and the other group is a group COR_9 in which R_9 is defined as indicated above for R'_9; and

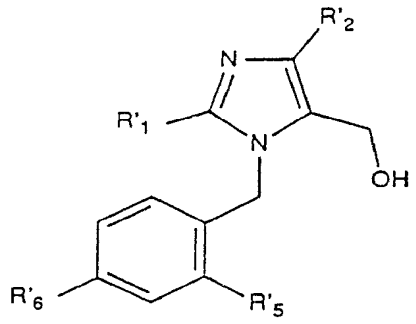
(vi) the compounds of formula I' in which R'_6 or R'_7 is a cyano group are converted to a compound of formula I in which R_6 or R_7 is a tetrazol-5-yl group by the methods known to those skilled in the art, especially by the 1,3-dipolar cycloaddition of trialkyltin or triaryltin azides.

To obtain the compounds of formula II', it is recommended to reduce an aldehyde of the formula



(IV)

in which R'_1, R'_2, R'_5 and R'_6 are defined as indicated above, by the methods known to those skilled in the art, especially by reaction with $NaBH_4$ or KBH_4 in an alcohol, to give an alcohol of the formula



(V)

in which R'_1, R'_2, R'_5 and R'_6 are defined as indicated above, and then to convert the resulting alcohol to a derivative of formula II', especially a chlorinated derivative, by the methods known to those skilled in the art, especially by reaction with thionyl chloride in an inert solvent such as a halogenated solvent.

The intermediates of formula IV in which:
(i) R'_1 is an n-propyl group, R'_2 is a hydrogen atom or a halogen, R'_5 is the hydrogen atom and R'_6 is a cyano group or a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group or a benzyloxy group, or
(ii) R'_1 is an n-butyl group, R'_2 and R'_5 are the hydrogen atom and R'_6 is a group COR'_9 in which R'_9 is a t-butoxy or benzyloxy group,
are novel compounds and form one of the subjects of the invention.

The intermediates of formula V in which R'_1 is a C_1-C_4-alkyl group, R'_2 is the hydrogen atom or a halogen, R'_5 is the hydrogen atom and R'_6 is a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group or a benzyloxy group are novel compounds and form one of the subjects of the invention.

The intermediates of formula II' in which R'_1 is an n-butyl group, R'_2 and R'_5 are the hydrogen atom and R'_6 is a group COR'_9 in which R'_9 is a t-butoxy or benzyloxy group are novel compounds and form one of the

subjects of the invention.

The invention will be understood more clearly from the description of the following Preparatory Examples, in which the Preparations refer to the intermediates and the Examples refer to the products according to the invention. These Examples are intended to illustrate the invention without limiting its scope.

PREPARATION 1

2-Butyl-4-iodo-1H-imidazole-5-carboxaldehyde

A solution of 70.5 g ($128.5 \cdot 10^{-3}$ mol) of ammoniacal cerium nitrate in 58 ml of water is added dropwise to a suspension, at 15°C, of 16 g ($57 \cdot 10^{-3}$ mol) of 2-butyl-4-iodo-1H-imidazole-5-methanol in 48 ml of acetic acid. The reaction mixture is stirred at room temperature for 24 hours. A 10 N solution of sodium hydroxide is then added until the pH is 6. The precipitate formed is extracted with ethyl acetate, washed with water and then dried over magnesium sulfate to give 14.7 g (yield: 93%) of a beige solid.

M.p. = 90°C

PREPARATION 2

Methyl 4-[(4-chloro-5-formyl-2-propyl-1H-imidazol-1-yl)methyl]benzoate

17.4 g ($126 \cdot 10^{-3}$ mol) of potassium carbonate are added to a solution of 18.15 g ($105 \cdot 10^{-3}$ mol) of 4-chloro-2-propyl-1H-imidazole-5-carboxaldehyde and 28.9 g ($126 \cdot 10^{-3}$ mol) of methyl 4-bromomethylbenzoate in 275 ml of dimethylformamide. The reaction mixture is heated at 40°C for 2 hours, with stirring, and then cooled, poured into water and extracted with ethyl acetate. The organic phases are washed with water until

the washings are neutral, dried over magnesium sulfate and concentrated. The crude solid obtained is recrystallized from ethanol to give 28 g (yield: 83%) of a white solid.

M.p. = 89°C

The products of Preparations 9, 10, 11 and 31 are obtained by an analogous procedure.

PREPARATION 3

Methyl 4-[(5-formyl-2-propyl-1H-imidazol-1-yl)methyl]-benzoate

7.1 g ($72 \cdot 10^{-3}$ mol) of potassium acetate and then, under nitrogen, 3.48 g of 5% palladium-on-charcoal are added to a solution of 23.2 g ($72 \cdot 10^{-3}$ mol) of methyl 4-[(4-chloro-5-formyl-2-propyl-1H-imidazol-1-yl)methyl]benzoate in 230 ml of methanol. The suspension obtained is stirred under a hydrogen atmosphere at room temperature for 3 days. The catalyst is filtered off, the methanol is evaporated off, the residue is taken up in ethyl acetate and the resulting solution is washed with water until the washings are neutral. After drying over magnesium sulfate, the solution is concentrated and the oily crude product obtained is chromatographed on silica using a cyclohexane/acetone mixture (7/3; v/v) as the eluent. Evaporation of the eluent gives 19 g (yield: 91.6%) of a white solid.

M.p. = 72°C

The following products were obtained by an analogous procedure:

1,1-Dimethylethyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (Preparation 12)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.89 (t, 3H); 1.31 (m, 2H); 1.57 (s, 9H); 1.69 (m, 2H); 2.66 (t, 2H); 5.82 (s, 2H); 7.03 (d, 2H); 7.81 (s, 1H);

7.93 (d, 2H); 9.66 (s, 1H).

Ethyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]-benzoate (Preparation 32)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.89 (t, 3H); 1.23 - 1.40 (m, 5H); 1.63 - 1.74 (m, 2H); 2.64 (t, 2H); 4.35 (q, 2H); 5.60 (s, 2H); 7.04 (d, 2H); 7.82 (s, 1H); 7.97 (d, 2H); 9.67 (s, 1H).

PREPARATION 4

Methyl 4-[(2-butyl-5-formyl-4-trifluoromethyl-1H-imidazol-1-yl)methyl]benzoate

A solution of 32 ml of dibromodifluoromethane in 32 ml of dimethylformamide is added in 2 hours to a suspension of 82 g of cadmium powder in 183 ml of dimethylformamide and room temperature. The reaction mixture is stirred for 2 hours at room temperature and then left to stand for 30 minutes. 8.34 g ($58 \cdot 10^{-3}$ mol) of cuprous bromide and then a solution of 7.08 g ($16.6 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-5-formyl-4-iodo-1H-imidazol-1-yl)methyl]benzoate in 50 ml of dimethylformamide are added to a mixture of 70 ml of the above solution in 75 ml of hexamethylphosphorotriamide at 0°C. The reaction mixture is heated at 70°C for 4 hours. After the mixture has cooled, 600 ml of water are added and extraction is carried out with ethyl acetate. The organic phases are washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting oil is purified by chromatography on silica using a toluene/ethyl acetate mixture (9/1; v/v) as the eluent to give 5.71 g (yield: 93%) of an ochre solid.

M.p. = 59°C

PREPARATION 5

4-[(2-Butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoic acid

25 ml of water and 3 g ($75 \cdot 10^{-3}$ mol) of sodium hydroxide are added to a solution of 16 g ($53.3 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-methyl]benzoate in 100 ml of methanol. The reaction mixture is refluxed for 5 hours. The methanol is evaporated off under reduced pressure and 150 ml of water are added to the residue. The mixture is washed with twice 50 ml of ethyl acetate. The aqueous phase is acidified to pH 6 with a 1 N solution of hydrochloric acid and extracted with 2 times 100 ml of an ethyl acetate/n-butanol mixture (80/20; v/v). The organic phases are washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give 14 g (yield: 94%) of a yellow solid.

M.p. = 148°C

The product of Preparation 33 is obtained by a procedure analogous to Preparation 5.

PREPARATION 6

Phenylmethyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-methyl]benzoate

5.4 g ($50 \cdot 10^{-3}$ mol) of benzyl alcohol, 5.85 g ($48 \cdot 10^{-3}$ mol) of 4-dimethylaminopyridine and 9.17 g ($48 \cdot 10^{-3}$ mol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride are added to a solution of 13.5 g ($47.2 \cdot 10^{-3}$ mol) of 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoic acid in a mixture of 5 ml of dimethylformamide and 200 ml of dichloromethane. The reaction mixture is stirred at room temperature for 20 hours and then washed with twice 60 ml of water.

The organic phase is dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue is purified by chromatography using a hexane/acetone mixture (70/30; v/v) as the eluent to give 17 g (yield: 95%) of a yellow oil.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.35 (m, 2H); 1.72 (m, 2H); 2.65 (t, 2H); 5.34 (s, 2H); 5.62 (s, 2H); 7.04 (d, 2H); 7.4 (m, 5H); 7.80 (s, 1H); 8.03 (d, 2H); 9.66 (s, 1H).

The product of Preparation 34 and the following products are obtained by an analogous procedure:

Pentyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]-benzoate (Preparation 35)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.89 (m, 6H); 1.18 - 1.40 (m, 5H); 1.62 - 1.77 (m, 5H); 2.63 (t, 2H); 4.29 (t, 2H); 5.63 (s, 2H); 7.05 (d, 2H); 7.81 (s, 1H); 7.97 (d, 2H); 9.67 (s, 1H).

Butyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]-benzoate (Preparation 36)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 0.96 (t, 3H); 1.31 - 1.49 (m, 4H); 1.64 - 1.78 (m, 4H); 2.63 (t, 2H); 4.30 (t, 2H); 5.62 (s, 2H); 7.04 (d, 2H); 7.81 (s, 1H); 7.97 (d, 2H); 9.67 (s, 1H).

2-Methylpropyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-methyl]benzoate (Preparation 37)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 0.99 (d, 6H); 1.31 - 1.38 (m, 2H); 1.64 - 1.75 (m, 2H); 2.06 (m, 1H); 2.63 (t, 2H); 4.08 (d, 2H); 5.63 (s, 2H); 7.05 (d, 2H); 7.81 (s, 1H); 7.98 (d, 2H); 9.67 (s, 1H).

Cyclopropylmethyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (Preparation 38)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.35 (m, 2H); 0.59 (m, 2H); 0.88 (t, 3H); 1.21 - 1.25 (m, 1H); 1.29 - 1.40 (m, 2H); 1.60 - 1.75 (m, 2H); 2.63

(t, 2H); 4.12 (d, 2H); 5.63 (s, 2H); 7.05 (d, 2H); 7.81 (s, 1H); 7.97 (d, 2H); 9.67 (s, 1H).

3-Methylbutyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-methyl]benzoate (Preparation 39)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 0.97 (d, 6H); 1.23 - 1.41 (m, 3H); 1.61 - 1.82 (m, 4H); 2.63 (t, 2H); 4.35 (t, 2H); 5.63 (s, 2H); 7.05 (d, 2H); 7.81 (s, 1H); 7.97 (d, 2H); 9.67 (s, 1H).

Phenylmethyl 4-[(2-butyl-4-chloro-5-formyl-1H-imidazol-1-yl)methyl]benzoate (Preparation 40)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.29 - 1.37 (m, 2H); 1.61 - 1.72 (m, 2H); 2.60 (t, 2H); 5.35 (s, 2H); 5.59 (s, 2H); 7.07 (d, 2H); 7.34 - 7.44 (m, 5H); 8.02 (d, 2H).

PREPARATION 62

Methyl 4-[[2-butyl-5-formyl-4-methylthio-1H-imidazol-1-yl]methyl]benzoate

3.24 g ($4.62 \cdot 10^{-2}$ mol) of sodium thiomethylate are added to a solution of 3.87 g ($1.15 \cdot 10^{-2}$ mol) of methyl 4-[(4-chloro-5-formyl-2-butyl-1H-imidazol-1-yl)-methyl]benzoate in 40 ml of methanol. The reaction mixture is refluxed for 4 hours, with stirring, and then cooled, poured into a 10% aqueous solution of citric acid at 0°C and extracted with ethyl acetate. The organic phases are washed with water until the washings are neutral, dried over magnesium sulfate and concentrated. The oily residue obtained is chromatographed on silica using a toluene/ethyl acetate mixture (8/2; v/v) as the eluent. Evaporation of the eluent gives 2.8 g (yield: 70%) of a yellow solid.

M.p. = 72 - 74°C

PREPARATION 7

Methyl 4-[(2-butyl-5-hydroxymethyl-1H-imidazol-1-yl)-methyl]benzoate

5.92 g ($19.7 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate are dissolved in 60 ml of methanol and the solution obtained is cooled with an ice bath. 895 mg ($23.6 \cdot 10^{-3}$ mol) of sodium borohydride are then added in portions over 30 minutes, with stirring. After 10 minutes, the methanol is evaporated off and the residue is diluted with water and extracted with methylene chloride. The combined organic phases are washed with water, dried over magnesium sulfate and concentrated to give 5.22 g (yield: 88%) of a white solid.

M.p. = 144°C

The products of Preparations 13 to 21 and 41 to 49 and the following product were prepared by an analogous procedure:

4-[(2-Butyl-5-hydroxymethyl-1H-imidazol-1-yl)methyl]-benzonitrile (Preparation 50)

M.p. = 109°C

PREPARATION 8

Methyl 4-[(2-butyl-5-chloromethyl-1H-imidazol-1-yl)-methyl]benzoate hydrochloride

5.2 g ($17.2 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-5-hydroxymethyl-1H-imidazol-1-yl)methyl]benzoate are dissolved in 50 ml of chloroform and the solution is cooled with an ice bath. 10.23 g ($86 \cdot 10^{-3}$ mol) of thionyl chloride are then added dropwise, with stirring. Stirring is maintained at this temperature for 15 minutes after the addition has ended. The chloroform is evaporated off and toluene is then added and

evaporated off to give 6.1 g (yield: 99.3%) of a beige solid.

M.p. = 158°C

The products of Preparations 22 to 29, 51 and 53 to 59 and the following products were obtained by an analogous procedure:

Methyl 4-[(2-butyl-5-chloromethyl-4-trifluoromethyl-1H-imidazol-1-yl)methyl]benzoate (Preparation 30)

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.33 (m, 2H); 1.68 (m, 2H); 2.60 (t, 2H); 3.92 (s, 3H); 4.52 (s, 2H); 5.29 (s, 2H); 7.06 (d, 2H); 8.03 (d, 2H).

4-[(2-Butyl-5-chloromethyl-1H-imidazol-1-yl)methyl]-benzonitrile hydrochloride (Preparation 60)

M.p. = 95°C

Phenylmethyl 4-[(2-butyl-4-chloro-5-chloromethyl-1H-imidazol-1-yl)methyl]benzoate (Preparation 61)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.27 - 1.39 (m, 2H); 1.62 - 1.72 (m, 2H); 2.55 (t, 2H); 4.44 (s, 2H); 5.24 (s, 2H); 5.36 (s, 2H); 7.05 (d, 2H); 7.16 - 7.45 (m, 5H); 8.05 (d, 2H).

PREPARATION 63

Pentyl 2-methyl-6-nitrobenzoate

6 ml (0.082 mol) of thionyl chloride are added to a suspension of 5 g (0.0276 mol) of 2-nitro-6-methylbenzoic acid in 90 ml of toluene. The reaction mixture is refluxed for 3.5 h, with stirring, and evaporated under reduced pressure. 45 ml of n-pentanol and then added to the oily residue and the mixture is refluxed for 2 hours, with stirring. After cooling, 100 ml of water are added, a saturated aqueous solution of sodium bicarbonate is added until the pH is basic,

and the mixture is extracted with toluene. The organic phases are washed with water, dried over magnesium sulfate and concentrated. After distillation of the n-pentanol under reduced pressure, 6.74 g of a yellow oil are obtained (yield: 97%).

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.89 (t, 3H); 1.36 (m, 4H); 1.77 (m, 2H); 2.45 (s, 3H); 4.37 (t, 2H); 7.43 (t, 1H); 7.53 (d, 1H); 8.00 (d, 1H).

PREPARATION 64

2-[(2-Aminobenzoyl)oxy]-N,N-dipropylacetamide

15 g (0.084 mol) of N,N-dipropylchloroacetamide, 1.26 g ($8.44 \cdot 10^{-3}$ mol) of sodium iodide and 11.1 g (0.1 mol) of triethylamine are added to a solution of 15 g (0.1 mol) of anthranilic acid in 150 ml of dimethylformamide. The mixture is stirred overnight at room temperature. A saturated solution of sodium bicarbonate is added and extraction is carried out with ethyl acetate. The organic phases are washed with water until the pH is neutral, dried over magnesium sulfate and concentrated. The oil obtained is crystallized by stirring in ether to give 7.86 g (yield: 33.4%) of the expected product.

M.p. = 64°C

The following products are obtained by a procedure analogous to Preparation 64:

2-[(2-Aminobenzoyl)oxy]pentan-3-one (Preparation 65)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.09 (t, 3H); 1.49 (d, 3H); 2.58 (m, 2H); 5.28 (q, 1H); 5.70 (s, 2H); 6.60 (m, 2H); 7.28 (m, 1H); 7.91 (m, 1H).

Ethyl 2-[(2-aminobenzoyl)oxy]acetate (Preparation 66)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.30 (t, 3H); 4.25 (q, 2H); 4.80 (s, 2H); 5.69 (s, 2H); 6.66 (m, 2H); 7.29 (m, 1H); 7.93 (m, 1H).

Pentyl 2-[(2-aminobenzoyl)oxy]acetate (Preparation 67)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (m, 3H); 1.28 (m, 4H); 1.63 (m, 2H); 4.16 (t, 2H); 4.80 (s, 2H); 5.68 (s, 2H); 6.65 (m, 2H); 7.28 (m, 1H); 7.92 (m, 1H).

PREPARATION 68

Cyclopropylmethyl 2-aminobenzoate

1.77 g (0.044 mol) of sodium hydroxide are added to a suspension of 9 g (0.0552 mol) of isatoic anhydride in 14.3 g (0.198 mol) of cyclopropylmethanol. The reaction mixture is heated at 80°C for 3 hours, with stirring, and then poured into water and extracted with ethyl acetate. The organic phases are washed with water until the pH of the washings is neutral, dried over magnesium sulfate and concentrated under reduced pressure to give 7.51 g (yield: 64%) of an ochre oil.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.34 (m, 2H); 0.61 (m, 2H); 1.25 (m, 1H); 4.10 (d, 2H); 5.70 (s, 2H); 6.65 (m, 2H); 7.25 (m, 1H); 7.92 (m, 1H).

The product of Preparation 69 and the following products are obtained by a procedure analogous to Preparation 68:

1-Methylpentyl 2-aminobenzoate (Preparation 70)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (m, 3H); 1.31 - 1.73 (m, 2H); 5.10 (m, 1H); 5.71 (s, 2H); 6.61 (m, 2H); 7.25 (m, 1H); 7.88 (m, 1H).

2-[N,N-Diethylamino]ethyl 2-aminobenzoate (Preparation 71)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.06 (t, 6H); 2.63 (q, 4H); 2.83 (t, 2H); 4.36 (t, 2H); 5.70 (s, 2H); 6.63 (m, 2H); 7.25 (s, 1H); 7.86 (d, 1H).

PREPARATION 72

2-[(2-Aminobenzoyl)oxy]-N,N-diethylpropionamide

2 g ($6.66 \cdot 10^{-2}$ mol) of NaH as an 80% suspension in oil are added to a solution of 8.31 g ($6.06 \cdot 10^{-2}$ mol) of anthranilic acid in 45 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-(1H)-pyrimidin-2-one (DMPU). The mixture is stirred at room temperature for 0.5 h and a solution of 10.91 g ($6.66 \cdot 10^{-2}$ mol) of N,N-diethyl-2-chloropropionamide in 10 ml of DMPU is then added dropwise. The reaction mixture is then stirred at 100°C for 1.5 h. After cooling, a saturated solution of sodium bicarbonate is added and the precipitate obtained is filtered off. After washing with water and drying, 14.31 g (yield: 89%) of the expected product are obtained.

M.p. = 134°C

The products of Preparations 73, 74 and 75 and the following products are obtained by a procedure analogous to Preparation 72:

1-[(2-Aminobenzoyl)oxy]ethyl 2-ethylbutanoate (Preparation 76)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.89 (t, 6H); 1.47 - 1.66 (m, 7H); 2.22 (m, 1H); 5.73 (s, 2H); 6.63 (m, 2H); 7.13 (q, 1H); 7.26 (m, 1H); 7.84 (m, 1H).

1-[(2-Aminobenzoyl)oxy]ethyl cyclopentylcarboxylate (Preparation 77)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.53 - 1.87 (m, 11H); 2.75 (m, 1H); 5.73 (s, 2H); 6.61 (t, 2H); 7.10 (q, 1H); 7.27 (m, 1H); 7.83 (m, 1H).

1-[(2-Aminobenzoyl)oxy]ethyl cyclohexylcarboxylate (Preparation 78)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.18 - 1.88 (m, 13H); 2.31 (m, 1H); 5.74 (s, 2H); 6.63

(m, 2H); 7.09 (m, 1H); 7.28 (m, 1H); 7.83 (m, 1H).

[(2-Aminobenzoyl)oxy]methyl hexanoate (Preparation 79)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.29 (m, 4H); 1.63 (m, 2H); 2.37 (t, 2H); 5.7 (s, 2H); 5.96 (s, 2H); 6.63 (m, 2H); 7.29 (m, 1H); 7.88 (d, 1H).

1-[(2-Aminobenzoyl)oxy]ethyl hexanoate (Preparation 80)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.26 (t, 3H); 1.30 (m, 4H); 1.60 (m, 5H); 2.35 (t, 2H); 5.76 (s, 2H); 6.63 (m, 2H); 7.11 (m, 1H); 7.27 (m, 1H); 7.86 (d, 1H).

1-[(2-Aminobenzoyl)oxy]ethyl cyclohexylacetate (Preparation 81)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.91 - 1.42 (m, 5H); 1.55 - 1.75 (m, 9H); 2.20 (m, 2H); 5.74 (s, 2H); 6.63 (m, 2H); 7.12 (m, 1H); 7.27 (m, 1H); 7.85 (m, 1H).

1-[(2-Aminobenzoyl)oxy]ethyl cyclopentylacetate (Preparation 82)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.15 (m, 2H); 1.58 (m, 7H); 1.81 (m, 2H); 2.23 (m, 1H); 2.35 (m, 2H); 5.73 (s, 2H); 6.61 (d, 1H); 7.09 - 7.29 (m, 2H); 7.85 (d, 1H).

[(2-Aminobenzoyl)oxy]methyl 2,2-dimethylpropionate (Preparation 83)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.49 (s, 9H); 4.69 (s, 2H); 5.66 (s, 2H); 6.65 (m, 2H); 7.27 (m, 1H); 7.93 (m, 1H).

PREPARATION 84

N-[3-(N,N-Dimethylamino)propyl]-2-aminobenzamide

8.16 g ($8 \cdot 10^{-2}$ mol) of N,N-dimethylpropanediamine are added slowly to 6.52 g ($4 \cdot 10^{-2}$ mol) of isatoic anhydride and the mixture is then heated at

80°C for 1 hour. After cooling, 150 ml of water are added and extraction is carried out with ethyl acetate. The organic phases are washed with water until the pH of the washings is neutral, dried over sodium sulfate, filtered and evaporated under reduced pressure to give 7.8 g (yield: 88%) of the expected product.

M.p. = 76°C

PREPARATION 85

N,N-Diethyl-2-[N-(2-aminobenzoyl)amino]acetamide

3.33 g ($2 \cdot 10^{-2}$ mol) of aminoacetic acid diethylamide and 3.03 g ($3 \cdot 10^{-2}$ mol) of triethylamine are added successively to a solution of 3.27 g ($2 \cdot 10^{-2}$ mol) of isatoic anhydride in 20 ml of dimethylformamide. The reaction mixture is subsequently heated at 70°C for 1 hour and then cooled, water is added and extraction is carried out with ethyl acetate. The organic phases are washed with water until the washings are neutral, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 3.34 g (yield: 67%) of the expected product.

M.p. = 62°C

The following product is obtained by a procedure analogous to Preparation 85:

Ethyl N-[2-aminobenzoyl]-L-valine (Preparation 86)

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

1.0 (t, 6H); 1.31 (t, 3H); 2.26 (m, 1H); 4.23 (m, 2H); 4.72 (m, 1H); 5.5 (s, 2H); 6.57 (d, 1H); 6.69 (m, 2H); 7.23 (t, 1H); 7.41 (d, 1H).

PREPARATION 87

Pentyl 2-amino-6-methylbenzoate

0.62 g of 10% palladium-on-charcoal is added

under a nitrogen atmosphere to a solution of 6.2 g (0.0247 mol) of pentyl 2-nitro-6-methylbenzoate in 200 ml of ethanol. The reaction medium is then placed under a hydrogen atmosphere and stirred for 6 hours. After filtration, the ethanol is evaporated off under reduced pressure to give 5.22 g (yield: 96%) of an ochre oil.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.92 (t, 3H); 1.38 (m, 4H); 1.73 (m, 2H); 2.44 (s, 3H); 4.32 (t, 2H); 5.2 (s, 2H); 5.54 (d, 2H); 7.07 (t, 1H).

PREPARATION 88

Pentyl 2-amino-6-chlorobenzoate

10.6 g (0.087 mol) of 4-dimethylaminopyridine, 16.6 g (0.087 mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 7.65 g (0.087 mol) of n-pentanol are added to a suspension of 15 g (0.087 mol) of 2-amino-6-chlorobenzoic acid in 250 ml of dichloromethane. The reaction mixture is stirred at room temperature for 20 hours and then washed with 1 x 50 ml of a 10% solution of citric acid followed by 2 x 50 ml of water. The organic phase is dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue is purified by flash chromatography on silica using a cyclohexane/acetone mixture (90/10; v/v) as the eluent to give 4.64 g (yield: 22%) of a yellow oil.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.92 (t, 3H); 1.38 (m, 4H); 1.72 (q, 2H); 4.33 (t, 2H); 4.84 (s, 2H); 6.55 (d, 1H); 6.73 (d, 1H); 7.07 (t, 1H).

A number of intermediates have been collated in Tables A, B, C and D, in which the symbols used are identical to those in Tables I to VII.

Example 1:

Methyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

8 g ($22.3 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-5-chloromethyl-1H-imidazol-1-yl)methyl]benzoate hydrochloride are suspended in 80 ml of anhydrous toluene. 10.15 g ($67.1 \cdot 10^{-3}$ mol) of methyl 2-aminobenzoate and then 4.79 g ($44.7 \cdot 10^{-3}$ mol) of 2,6-dimethylpyridine are added. The reaction mixture is refluxed for 8 hours and then poured into iced water. The aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with water until the washings are neutral, dried over magnesium sulfate and concentrated to give 11.8 g of a brown oil, which is purified by chromatography using a toluene/isopropanol mixture (9/1; v/v) as the eluent. After evaporation of the eluates, 9 g (yield: 92.3%) of an orange oil are obtained.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.34 (m, 2H); 1.68 (m, 2H); 2.56 (t, 2H); 3.77 (s, 3H); 3.91 (s, 3H); 4.19 (d, 2H); 5.18 (s, 2H); 6.58 - 6.67 (m, 2H); 6.92 (d, 2H); 7.04 (s, 1H); 7.30 (t, 1H), 7.67 (t, 1H); 7.82 (d, 1H); 7.91 (d, 2H).

The products of Examples 2, 76, 88, 89, 98, 219, 220, 222 and 225 and the following products were prepared by an analogous procedure:

Example 3:

Methyl 2-[[[2-propyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

Brown oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.94 (t, 3H); 1.73 (m, 2H); 2.53 (t, 2H); 3.77 (s, 3H);

3.91 (s, 3H); 4.18 (d, 2H); 5.18 (s, 2H); 6.58 - 6.67 (m, 2H); 6.92 (d, 2H); 7.05 (s, 1H); 7.28 - 7.33 (m, 1H); 7.68 (t, 1H); 7.82 (d, 1H); 7.90 (d, 2H).

Example 4:

2,2-Dimethyl-1,3-dioxolan-4-ylmethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

Oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.33 (m, 2H); 1.37 (s, 3H); 1.43 (s, 3H); 1.72 (m, 2H); 2.55 (t, 3H); 3.82 (m, 1H); 4.10 (m, 1H); 4.25 (m, 4H); 4.35 (m, 1H); 5.18 (s, 2H); 5.35 (s, 2H); 6.62 (m, 2H); 6.93 (d, 2H); 7.04 (s, 1H); 7.26 - 7.46 (m, 6H); 7.64 (t, 1H); 7.85 (d, 1H); 7.94 (d, 2H).

Example 5:

Phenylmethyl 2-[[[2-butyl-1-[(4-(1,1-dimethylethoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

Orange oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.32 (m, 2H); 1.56 (s, 9H); 1.73 (m, 2H); 2.56 (m, 2H); 4.18 (d, 2H); 5.18 (s, 2H); 5.23 (s, 2H); 6.60 (m, 2H); 6.89 (d, 2H); 7.03 (s, 1H); 7.37 (m, 6H); 7.70 (t, 1H); 7.90 (m, 3H).

Example 6:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-3,5-dichlorobenzoate

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (t, 3H); 1.28 (m, 2H); 1.66 (m, 2H); 2.55 (t, 2H); 3.85 (s, 3H); 3.91 (s, 3H); 4.12 (d, 2H); 5.28 (s, 2H); 6.71 (t, 1H); 6.98 (d, 2H); 7.40 (d, 1H); 7.78 (d, 1H); 7.97 (d, 2H).

Example 7:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-3-methyl-benzoate

Pale yellow oil

^{1}H NMR (300 MHz; dimethyl sulfoxide; ppm)
0.79 (t, 3H); 1.24 (m, 2H); 1.48 (m, 2H); 2.25 (s, 3H); 2.50 (t, 2H); 3.73 (s, 3H); 3.83 (s, 3H); 4.03 (d, 2H); 5.30 (s, 2H); 6.40 (t, 1H); 6.85 (t, 1H); 7.06 (d, 2H); 7.29 (d, 1H); 7.59 (d, 1H); 7.90 (d, 2H).

Example 8:

Methyl N-[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]-N-methyl-2-aminobenzoate

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (t, 3H); 1.34 (m, 2H); 1.68 (m, 2H); 2.57 (t, 2H); 2.61 (s, 3H); 3.85 (s, 3H); 3.89 (s, 3H); 3.93 (s, 2H); 5.32 (s, 2H); 6.88 - 6.99 (m, 4H); 7.35 (t, 1H); 7.68 (d, 1H); 7.88 (d, 2H).

Example 74:

Pentyl 2-[[[2-butyl-4-chloro-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.88 (m, 6H); 1.28 - 1.38 (m, 6H); 1.60 - 1.71 (m, 4H); 2.51 (t, 2H); 4.12 (t, 2H); 4.18 (d, 2H); 5.19 (s, 2H); 5.35 (s, 2H); 6.60 (t, 1H); 6.67 (d, 1H); 6.90 (d, 2H); 7.32 - 7.45 (m, 5H); 7.75 (t, 1H); 7.79 (d, 1H); 7.90 (d, 2H).

Example 75:

Methyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-4-methylthio-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.31 (m, 2H), 1.68 (m, 2H); 2.46 (s, 3H); 2.54 (t, 2H); 3.75 (s, 3H); 3.91 (s, 3H); 4.30 (d, 2H); 5.19 (s, 2H); 6.60 (t, 1H); 6.80 (d, 1H); 6.89 (d, 2H); 7.32 (m, 1H); 7.67 (t, 1H); 7.82 (m, 3H).

Example 77:

((Dipropylamino)carbonyl)methyl 2-[[[2-butyl-1-[4-((methoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.92 (m, 9H); 1.33 (m, 2H); 1.52 - 1.74 (m, 6H); 2.55 (t, 2H); 3.17 (t, 2H); 3.30 (t, 2H); 3.90 (s, 3H); 4.17 (d, 2H); 4.83 (s, 2H); 5.19 (s, 2H); 6.63 (m, 2H); 6.92 (d, 2H); 7 (s, 1H); 7.33 (t, 1H); 7.61 (t, 1H); 7.90 (d, 2H); 7.96 (d, 1H).

Example 78:

((N,N-Dipropylamino)carbonyl)methyl 2-[[[2-butyl-1-[4-((benzyloxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.84 - 0.98 (m, 9H); 1.35 (m, 2H); 1.53 - 1.71 (m, 6H); 2.55 (t, 2H); 3.15 (t, 2H); 3.29 (t, 2H); 4.16 (d, 2H); 4.79 (s, 2H); 5.19 (s, 2H); 5.35 (s, 2H); 6.60 (m, 2H); 6.91 (d, 2H); 7 (s, 1H); 7.16 - 7.45 (m, 6H); 7.59 (t, 1H); 7.93 - 7.97 (m, 3H).

Example 79:

((N,N-Diethylamino)carbonyl)methyl 2-[[[2-butyl-1-[4-((benzyloxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (t, 3H); 1.14 (t, 3H); 1.23 (t, 3H); 1.35 (m, 2H); 1.68 (m, 2H); 2.54 (t, 2H); 3.25 (q, 2H); 3.38 (q, 2H); 4.16 (d, 2H); 4.78 (d, 2H); 5.19 (s, 2H); 5.35 (s, 2H); 6.61 (m, 2H); 6.90 (d, 2H); 7 (s, 1H); 7.16 - 7.45 (m, 6H); 7.58 (t, 1H); 7.95 (m, 3H).

Example 80:

1-((N,N-Diethylamino)carbonyl)ethyl 2-[[[2-butyl-1-[4-((benzyloxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (t, 3H); 1.12 (t, 3H); 1.24 (t, 3H); 1.33 (m, 2H); 1.47 (d, 3H); 1.68 (m, 2H); 2.55 (t, 2H); 3.23 - 3.52 (m, 4H); 4.14 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 5.40 (q, 1H); 6.60 (m, 2H); 6.93 (d, 2H); 7 (s, 1H); 7.16 - 7.45 (m, 6H); 7.57 (t, 1H); 7.94 (m, 3H).

Example 81:

((N,N-Di(2-hydroxyethyl)amino)carbonyl)methyl 2-[[[2-butyl-1-[4-((benzyloxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 1.34 (m, 2H); 1.67 (m, 4H); 2.54 (t, 2H); 3.43 (t, 2H); 3.54 (t, 2H); 3.81 (t, 2H); 3.86 (t, 2H); 4.15 (d, 2H); 4.89 (s, 2H); 5.16 (s, 2H); 5.35 (s, 2H); 6.60 (m, 2H); 6.90 (d, 2H); 7 (s, 1H); 7.26 - 7.45 (m, 7H); 7.93 (m, 3H).

Example 82:

((N-Methyl-N-(2-hydroxyethyl)amino)carbonyl)methyl 2-[[[2-butyl-1-[4-((benzyloxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.77 (t, 3H); 1.22 (m, 2H); 1.47 (m, 2H); 2.49 (m, 2H); 2.81 (s, 1.5H); 2.95 (s, 1.5H); 3.45 (m, 2H); 3.54 (m, 2H); 4.32 (d, 2H); 4.74 (s, 1H); 4.87 (s, 1H); 5.32 (s, 2H); 5.34 (s, 2H); 6.55 (m, 2H); 6.81 (d, 2H); 6.88 (s, 1H); 6.95 (m, 2H); 7.40 (m, 4H); 7.58 (t, 1H); 7.72 (d, 1H); 7.85 (m, 2H).

Example 83:

Pentyl 6-chloro-2-[[[2-butyl-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.36 (m, 6H); 1.65 (m, 4H); 2.58 (t, 2H); 3.91 (s, 3H); 4.09 (d, 2H); 4.25 (t, 2H); 5.16 (s, 2H); 5.93 (t, 1H); 6.51 (d, 1H); 6.71 (d, 1H); 6.95 (d, 2H); 7.02 (s, 1H); 7.11 (t, 1H); 7.96 (d, 2H).

Example 84:

Ethyl [[2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]phenyl]-carbonyloxy]acetate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.29 (m, 5H); 1.69 (m, 2H); 2.17 (s, 2H); 2.58 (t, 2H); 4.22 (m, 4H); 4.71 (s, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.61 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.38 (m, 4H); 7.46 (t, 1H); 7.93 (m, 3H).

Example 85:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl 2-ethylbutanoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (m, 9H); 1.33 (m, 2H); 1.46 - 1.74 (m, 9H); 2.18 (m, 1H); 2.23 (t, 2H); 4.15 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.65 (m, 2H); 7.02 (d, 2H); 7.05 (t, 2H); 7.26 - 7.44 (m, 6H); 7.69 (t, 1H); 7.80 (m, 1H); 7.96 (d, 2H).

Example 86:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl cyclopentylcarboxylate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.36 (m, 2H); 1.2 - 1.8 (m, 13H); 2.5 (t, 2H); 2.67 (q, 1H); 4.17 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.61 (m, 2H); 6.90 (d, 2H); 7.02 (m, 2H); 7.16 - 7.42 (m, 6H); 7.7 (t, 1H); 7.82 (m, 1H); 7.93 (d, 2H).

Example 87:

Pentyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]-6-methylbenzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.38 (m, 6H); 1.64 (m, 4H); 2.40 (s, 3H); 2.54 (t, 2H); 3.90 (s, 3H); 4.12 (d, 2H); 4.19 (t, 2H); 5.18 (s, 2H); 6.50 (d, 2H); 6.68 (t, 1H); 6.92 (d, 2H); 7.03 (s, 1H); 7.14 (t, 1H); 7.92 (d, 2H).

Example 90:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl cyclopentylacetate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 1.15 (m, 2H); 1.35 (m, 2H); 1.45 - 1.90 (m, 12H); 2.1 - 2.35 (m, 3H); 2.56 (t, 2H); 4.17 (d, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 6.58 (m, 2H); 6.93 (d, 2H); 7.05 (m, 2H); 7.26 - 7.45 (m, 5H); 7.67 (t, 1H); 7.80 (d, 1H); 7.93 (d, 2H).

Example 91:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl cyclohexylcarboxylate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.21 - 1.74 (m, 15H); 1.86 (m, 2H); 2.26 (m, 1H); 2.53 (t, 2H); 4.15 (d, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 6.61 (m, 2H); 6.9 (d, 2H); 7.1 (m, 2H); 7.15 - 7.45 (m, 6H); 7.65 (t, 1H); 7.8 (m, 1H); 7.93 (d, 2H).

Example 92:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl 2,2-dimethylpropionate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.19 (s, 9H); 1.36 (m, 2H); 1.54 (d, 3H); 1.67 (m, 2H); 2.55 (t, 2H); 4.17 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.70 (m, 2H); 6.90 (d, 2H); 7.02 (m, 2H); 7.26 - 7.45 (m, 7H); 7.7 (t, 1H); 7.82 (m, 1H); 7.96 (d, 2H).

Example 93:

[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]methyl 2,2-dimethylpropionate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.33 (m, 2H); 1.47 (s, 9H); 1.69 (m, 3H); 2.56 (t, 2H); 4.17 (d, 2H); 4.57 (s, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.62 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.30 - 7.50 (m, 5H); 7.53 (t, 1H); 7.92 (m, 3H).

Example 94:

[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]methyl hexanoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (m, 6H); 1.20 - 1.8 (m, 10H); 2.34 (t, 2H); 2.56 (t, 2H); 4.17 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 5.84 (s, 2H); 6.59 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.29 - 7.45 (m, 6H); 7.58 (t, 1H); 7.84 (m, 1H); 7.96 (d, 2H).

Example 95:

2-(N,N-Diethylamino)ethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.05 (t, 6H); 1.27 (m, 2H); 1.65 (m, 2H); 2.59 (m, 6H); 2.78 (t, 2H); 4.08 - 4.26 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.62 (m, 2H); 6.91 (d, 2H); 7.03 (s, 1H); 7.26 - 7.50 (m, 6H); 7.71 (t, 1H); 7.83 (m, 1H); 7.93 (d, 2H).

Example 96:

1-Methylpentyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.24 - 1.38 (m, 9H); 1.68 (m, 4H); 2.54 (t, 2H); 4.16 (d, 2H); 4.98 (m, 1H); 5.19 (s, 2H); 5.34 (s, 2H); 6.60 (m, 2H); 6.93 (d, 2H); 7.03 (s, 1H); 7.29 - 7.42 (m, 6H); 7.78 (t, 1H); 7.86 (m, 1H); 7.94 (d, 2H).

Example 97:

1-Methyl-2-oxobutyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.84 (m, 3H); 1.05 (m, 3H); 1.30 - 1.71 (m, 7H); 2.54 (m, 4H); 4.18 (d, 2H); 5.17 (m, 3H); 5.35 (s, 2H); 6.62 (m, 2H); 6.93 (s, 2H); 7.03 (s, 1H); 7.26 - 7.41 (m, 5H); 7.45 (t, 1H); 7.93 (m, 3H).

Example 99:

2-Oxobutyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.12 (t, 3H); 1.30 (m, 3H); 1.69 (m, 2H); 2.43 (m, 2H); 2.55 (m, 2H); 4.17 (d, 2H); 4.74 (s, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.59 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.30 - 7.42 (m, 5H); 7.46 (t, 1H); 7.91 (m, 3H).

Example 100:

Ethyl 2-[[2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]phenyl]-carbonyloxy]propionate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (t, 3H); 1.23 - 1.40 (m, 5H); 1.54 (d, 3H); 1.69 (m, 2H); 2.55 (t, 2H); 4.17 (m, 4H); 5.13 (m, 3H); 5.35 (s, 2H); 6.59 (m, 2H); 6.64 (d, 2H); 7.02 (s, 1H); 7.27 - 7.40 (m, 6H); 7.44 (t, 1H); 7.93 (m, 3H).

Example 101:

Pentyl [[2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]phenyl]-carbonyloxy]acetate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (m, 6H); 1.31 (m, 6H); 1.62 (m, 4H); 2.56 (t, 2H); 4.16 (m, 4H); 4.67 (s, 2H); 5.15 (s, 2H); 5.42 (s, 2H); 6.63 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.27 - 7.46 (m, 6H); 7.50 (t, 1H); 7.95 (m, 3H).

Example 102:

2-Phenylethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.33 (m, 2H); 1.69 (m, 2H); 2.55 (t, 2H); 2.98 (t, 2H); 4.16 (d, 2H); 4.35 (t, 2H); 5.17 (s, 2H); 5.33 (s, 2H); 6.60 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.2 - 7.45 (m, 11H); 7.67 (t, 1H); 7.77 (m, 1H); 7.93 (d, 2H).

Example 103:

Phenyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 1.29 (m, 2H); 1.65 (m, 2H); 2.52 (t, 2H); 4.20 (d, 2H); 5.15 (s, 2H); 5.35 (s, 2H); 6.75 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.08 (m, 2H); 7.25 - 7.45 (m, 9H); 7.65 (t, 1H); 7.91 (d, 2H); 8.05 (m, 1H).

Example 104:

2-Methoxyethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.31 (m, 2H); 1.67 (m, 2H); 2.56 (t, 2H); 3.38 (s, 3H); 3.64 (t, 2H); 4.17 (d, 2H); 4.30 (t, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 6.60 (m, 2H); 6.94 (d, 2H); 7.04 (s, 1H); 7.25 - 7.45 (m, 6H); 7.64 (t, 1H); 7.86 (m, 1H); 7.93 (d, 2H).

Example 105:

Decyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (m, 6H); 1.30 (m, 20H); 1.66 (m, 2H); 2.55 (t, 2H); 4.14 (m, 4H); 5.18 (s, 2H); 5.33 (s, 2H); 6.57 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.26 - 7.45 (m, 4H); 7.7 (t, 1H); 7.85 (m, 1H); 7.94 (d, 2H).

Example 106:

Heptyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (m, 6H); 1.30 (m, 10H); 1.66 (m, 4H); 2.55 (t, 2H); 4.14 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.57 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.28 - 7.45 (m, 6H); 7.27 (t, 1H); 7.84 (m, 1H); 7.93 (d, 2H).

Example 107:

3-Methylbutyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 0.93 (d, 6H); 1.30 (m, 2H); 1.55 (m, 5H); 2.55 (t, 2H); 4.18 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.57 (m, 2H); 6.91 (d, 2H); 7.04 (s, 1H); 7.27 - 7.45 (m, 6H); 7.73 (t, 1H); 7.83 (m, 1H); 7.96 (d, 2H).

Example 108:

1-Methylethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.29 (d, 6H); 1.35 (m, 2H); 1.66 (m, 2H); 2.54 (t, 2H); 4.17 (d, 2H); 5.06 (m, 1H); 5.18 (s, 2H); 5.30 (s, 2H); 6.59 (m, 2H); 6.90 (d, 2H); 7.03 (s, 1H); 7.26 - 7.45 (m, 6H); 7.75 (t, 1H); 7.85 (m, 1H); 7.93 (d, 2H).

Example 109:

Cyclopropylmethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.29 (m, 2H); 0.55 (m, 2H); 0.87 (t, 3H); 1.1 - 1.38 (m, 3H); 1.68 (m, 2H); 2.52 (t, 2H); 3.97 (d, 2H); 4.17 (d, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 6.60 (m, 2H); 6.95 (d, 2H); 7.03 (s, 1H); 7.26 - 7.45 (m, 6H); 7.69 (t, 1H); 7.90 (m, 1H); 7.93 (d, 2H).

Example 110:

2-Methylpropyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (t, 3H); 0.96 (d, 6H); 0.33 (m, 2H); 1.69 (m, 2H); 2.0 (m, 1H); 2.55 (t, 2H); 3.93 (d, 2H); 4.17 (d, 2H); 5.19 (s, 2H); 5.34 (s, 2H); 6.60 (m, 2H); 6.91 (d, 2H); 7.04 (s, 1H); 7.28 - 7.45 (m, 6H); 7.72 (t, 1H); 7.87 (m, 1H); 7.93 (d, 2H).

Example 111:

Hexadecyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (m, 6H); 1.20 - 1.74 (m, 32H); 2.55 (t, 2H); 4.16 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.59 (m, 2H); 6.95 (d, 2H); 7.03 (s, 1H); 7.26 - 7.44 (m, 6H); 7.72 (t, 1H); 7.84 (m, 1H); 7.93 (d, 2H).

Example 112:

Butyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 0.95 (t, 3H); 1.38 (m, 4H); 1.67 (m, 4H); 2.55 (t, 2H); 4.17 (m, 4H); 6.19 (s, 2H); 5.35 (s, 2H); 6.60 (m, 2H); 6.91 (d, 2H); 7.04 (s, 1H); 7.27 - 7.45 (m, 6H); 7.72 (t, 1H); 7.82 (m, 1H); 7.95 (d, 2H).

Example 113:

Ethyl 2-[[[2-butyl-1-[(4-(ethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.36 (m, 8H); 1.69 (m, 2H); 2.55 (t, 2H); 4.19 (m, 4H); 4.37 (q, 2H); 5.18 (s, 2H); 6.60 (m, 2H); 6.90 (d, 2H); 7.04 (s, 1H); 7.30 (m, 1H); 7.74 (t, 1H); 7.84 - 7.92 (m, 3H).

Example 114:

Pentyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (m, 6H); 1.36 (m, 6H); 1.74 (m, 4H); 2.55 (t, 2H); 3.90 (s, 3H); 4.16 (m, 4H); 5.19 (s, 2H); 6.64 (m, 2H); 6.94 (d, 2H); 7.04 (s, 1H); 7.30 (m, 1H); 7.73 (t, 1H); 7.83 - 7.92 (m, 3H).

Example 115:

Pentyl 2-[[[1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-2-propyl-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.90 (m, 6H); 1.40 (m, 4H); 1.64 (m, 4H); 2.53 (t, 2H); 4.16 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.59 (m, 2H); 6.93 (d, 2H); 7.04 (s, 1H); 7.28 - 7.45 (m, 6H); 7.72 (t, 1H); 7.85 (m, 1H); 7.96 (d, 2H).

Example 116:

Methyl 2-[[[1-[(4-(methoxycarbonyl)phenyl)methyl]-2-propyl-1H-imidazol-5-yl]methyl]amino]-4-nitrobenzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.95 (t, 3H); 1.74 (m, 2H); 2.56 (t, 2H); 3.81 (s, 3H); 4.02 (s, 3H); 4.28 (d, 2H); 5.17 (s, 2H); 6.91 (d, 2H); 7.10 (s, 1H); 7.35 (m, 1H); 7.74 (m, 1H); 7.92 (m, 4H).

Example 117:

Methyl 2-[[[2-butyl-1-[(4-((1,1-dimethylethoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-4-nitrobenzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.35 (m, 2H); 1.58 (s, 9H); 1.69 (m, 2H); 2.58 (t, 2H); 3.81 (s, 3H); 4.26 (d, 2H); 5.16 (s, 2H); 6.87 (d, 2H); 7.09 (s, 1H); 7.37 (m, 1H); 7.47 (m, 1H); 7.82 - 7.95 (m, 4H).

Example 118:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl hexanoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.31 (m, 6H); 1.52 (d, 3H); 1.62 (m, 4H); 2.30 (t, 2H); 2.55 (t, 2H); 4.16 (d, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 6.56 (m, 2H); 6.90 (d, 2H); 7.03 (m, 2H); 7.27 - 7.45 (m, 6H); 7.66 (t, 1H); 7.82 (m, 1H); 7.93 (d, 2H).

Example 119:

1,1-Dimethylethyl 2-[[[2-butyl-1-[(4-(phenylmethoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.25 (m, 2H); 1.44 (s, 9H); 1.66 (m, 2H); 2.55 (t, 2H); 4.18 (d, 2H); 5.19 (s, 2H); 5.35 (s, 2H); 6.55 (m, 2H); 6.90 (d, 2H); 7.04 (s, 1H); 7.2 - 7.45 (m, 6H); 7.76 (m, 2H); 7.96 (d, 2H).

Example 120:

Ethyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.32 (m, 5H); 1.71 (m, 2H); 2.57 (t, 2H); 4.15 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.59 (m, 2H); 6.90 (d, 2H); 7.04 (s, 1H); 7.25 - 7.45 (m, 6H); 7.71 (t, 1H); 7.81 (m, 1H); 7.92 (d, 2H).

Example 121:

1-((Pentylcarbonyl)oxy)ethyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]-amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 6H); 1.32 (m, 6H); 1.54 (d, 3H); 1.67 (m, 4H); 2.31 (t, 2H); 2.56 (t, 2H); 3.90 (s, 3H); 4.18 (d, 2H); 5.18 (s, 2H); 6.58 (m, 2H); 6.94 (d, 2H); 7.03 (m, 2H); 7.35 (m, 1H); 7.66 (t, 1H); 7.82 (m, 1H); 7.92 (d, 2H).

Example 122:

Pentyl 2-[[[2-butyl-1-[(4-(phenylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.33 (m, 6H); 1.68 (m, 4H); 2.55 (t, 2H); 4.14 (m, 4H); 5.18 (s, 2H); 5.35 (s, 2H); 6.59 (m, 2H); 6.93 (d, 2H); 7.04 (s, 1H); 7.26 - 7.45 (m, 6H); 7.72 (t, 1H); 7.82 (m, 1H); 7.93 (d, 2H).

Example 123:

1-[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]ethyl cyclohexylacetate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 0.95 (m, 2H); 1.10 - 1.39 (m, 4H); 1.52 (d, 3H); 1.57 (m, 9H); 2.17 (m, 2H); 2.55 (t, 2H); 4.17 (d, 2H); 5.17 (s, 2H); 5.35 (s, 2H); 6.56 (m, 2H); 6.90 (d, 2H); 7.02 (m, 2H); 7.15 - 7.45 (m, 6H); 7.68 (t, 1H); 7.82 (m, 1H); 7.96 (d, 2H).

Example 124:

Phenylmethyl 2-[[[2-butyl-1-[(4-(pentoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.88 (m, 6H); 1.37 (m, 6H); 1.65 - 1.75 (m, 4H); 2.56 (t, 2H); 4.20 (d, 2H); 4.27 (t, 2H); 5.17 (s, 2H); 5.22 (s, 2H); 6.60 (t, 1H); 6.64 (d, 1H); 7.0 (s, 1H); 7.26 - 7.39 (m, 6H); 7.69 (t, 1H); 7.88 - 7.93 (m, 3H).

Example 125:

Phenylmethyl 2-[[[2-butyl-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (t, 3H); 1.33 (m, 2H); 1.69 (m, 2H); 2.55 (t, 2H); 3.87 (s, 3H); 4.16 (d, 2H); 5.17 (s, 2H); 5.21 (s, 2H); 6.58 (t, 1H); 6.64 (d, 1H); 6.90 (d, 2H); 7.04 (s, 1H); 7.26 - 7.41 (m, 6H); 7.66 (t, 1H); 7.88 - 7.92 (m, 3H).

Example 126:

Phenylmethyl 2-[[[2-butyl-1-[(4-(ethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (t, 3H); 1.33 (m, 5H); 1.69 (m, 2H); 2.56 (t, 2H); 4.18 (d, 2H); 4.33 (q, 2H); 5.17 (s, 2H); 5.22 (s, 2H); 6.60 (t, 1H); 6.64 (d, 1H); 6.91 (d, 2H); 7.05 (s, 1H); 7.26 - 7.41 (m, 6H); 7.70 (t, 1H); 7.88 - 7.97 (m, 3H).

Example 127:

Phenylmethyl 2-[[[2-butyl-1-[(4-(butoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.83 - 0.98 (m, 6H); 1.28 - 1.48 (m, 4H); 1.65 - 1.73 (m, 4H); 2.56 (t, 2H); 4.16 (d, 2H); 4.26 (t, 2H); 5.17 (s, 2H); 5.21 (s, 2H); 6.57 (t, 1H); 6.62 (d, 1H); 6.90 (d, 2H); 7.04 (s, 1H); 7.26 - 7.39 (m, 6H); 7.70 (t, 1H); 7.91 (m, 3H).

Example 128:

Phenylmethyl 2-[[[2-butyl-1-[(4-(hexadecyloxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (m, 6H); 1.25 - 1.41 (m, 28H); 1.64 - 1.76 (m, 4H); 2.56 (t, 2H); 4.18 (d, 2H); 4.26 (t, 2H); 5.17 (s, 2H); 5.22 (s, 2H); 6.58 (t, 1H); 6.64 (d, 1H); 6.90 (d, 2H); 7.04 (s, 1H); 7.26 - 7.39 (m, 6H); 7.70 (t, 1H); 7.88 - 7.93 (m, 3H).

Example 129:

Phenylmethyl 2-[[[2-butyl-1-[(4-((2-methylpropyl)oxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 0.96 (d, 6H); 1.29 - 1.41 (m, 2H); 1.65 - 1.75 (m, 2H); 2.04 (m, 1H); 2.56 (t, 2H); 4.05 (d, 2H); 4.18 (d, 2H); 5.18 (s, 2H); 5.22 (s, 2H); 6.60 (t, 1H); 6.65 (d, 1H); 6.91 (d, 2H); 7.04 (s, 1H); 7.26 - 7.39 (m, 6H); 7.70 (t, 1H); 7.89 - 7.94 (m, 3H).

Example 130:

Phenylmethyl 2-[[[2-butyl-1-[(4-(cyclopropylmethoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.36 (q, 2H); 0.58 (q, 2H); 0.86 (t, 3H); 1.19 - 1.39 (m, 3H); 1.68 - 1.75 (m, 2H); 2.56 (t, 2H); 4.10 (d, 2H); 4.18 (d, 2H); 5.18 (s, 2H); 5.22 (s, 2H); 6.60 (t, 1H); 6.64 (d, 1H); 6.91 (d, 2H); 7.04 (s, 1H); 7.26 - 7.41 (m, 6H); 7.68 (t, 1H); 7.89 - 7.96 (m, 3H).

Example 131:

Phenylmethyl 2-[[[2-butyl-1-[(4-((3-methylbutyl)oxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 0.94 (d, 6H); 1.25 - 1.41 (m, 2H); 1.59 - 1.80 (m, 5H); 2.56 (t, 2H); 4.18 (d, 2H); 4.30 (t, 2H); 5.17 (s, 2H); 5.22 (s, 2H); 6.60 (t, 1H); 6.64 (d, 1H); 6.90 (d, 2H); 7.04 (s, 1H); 7.26 - 7.39 (m, 6H); 7.70 (t, 1H); 7.88 - 7.93 (m, 3H).

Example 132:

Pentyl 2-[[[2-butyl-1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.84 - 0.95 (m, 6H); 1.31 - 1.42 (m, 6H); 1.64 - 1.75 (m, 4H); 2.52 (t, 2H); 4.15 (t, 2H); 4.20 (d, 2H); 5.19 (s, 2H); 6.62 (t, 1H); 6.66 (d, 1H); 6.90 (d, 2H); 7.07 (s, 1H); 7.31 (t, 1H); 7.47 (d, 2H); 7.68 (t, 1H); 7.83 (d, 1H).

Example 133:

Pentyl 2-[[[2-butyl-1-[(4-((1,1-dimethylethoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-4-nitrobenzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.84 - 0.95 (m, 6H); 1.25 - 1.42 (m, 6H); 1.58 (s, 9H); 1.62 - 1.76 (m, 4H); 2.57 (t, 2H); 4.21 (t, 2H); 4.23 (d, 2H); 5.13 (s, 2H); 6.88 (d, 2H); 7.08 (s, 1H); 7.38 (d, 1H); 7.45 (s, 1H); 7.85 (d, 2H); 7.95 (d, 2H).

Example 221:

Ethyl 3-methyl-2-[[[2-[[[2-butyl-1-[(4-(phenylmethoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-phenyl]carbonyl]amino]butanoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 0.97 (m, 6H); 1.32 (m, 5H); 1.70 (m, 2H); 2.20 (m, 1H); 2.53 (t, 2H); 4.11 (d, 2H); 4.23 (m, 2H); 4.60 (m, 1H); 5.19 (s, 2H); 5.35 (s, 2H); 6.51 (d, 1H); 6.63 (t, 2H); 6.96 (d, 2H); 7.0 (s, 1H); 7.26 (t, 1H); 7.40 (m, 6H); 7.52 (t, 1H); 7.95 (d, 2H).

Example 9:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-3,4,5-trimethoxybenzoate

4.82 g ($20 \cdot 10^{-3}$ mol) of methyl 2-amino-3,4,5-trimethoxybenzoate are added to a solution of 3.55 g ($9.06 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-4-chloro-5-chloromethyl-1H-imidazol-1-yl)methyl]benzoate hydrochloride in 30 ml of N-methylpyrrolidone. The reaction mixture is heated at 80°C for 5 hours. After the addition of 100 ml of water, the aqueous phase is extracted with 2 times 60 ml of ethyl acetate. The organic phases are washed with water until the pH of the washings is neutral, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The oily residue obtained is purified by chromatography using a toluene/ethyl acetate mixture (85/15; v/v) as the

eluent to give 2.43 g (yield: 48%) of a yellow oil.
^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.28 (m, 2H); 1.63 (m, 2H); 2.48 (t, 2H); 3.65 (s, 3H); 3.81 (s, 3H); 3.82 (s, 3H); 3.91 (s, 3H); 3.92 (s, 3H); 4.34 (s, 2H); 5.27 (s, 2H); 6.73 (s, 1H); 6.98 (d, 2H); 7.17 (s, 1H); 7.95 (d, 2H).

Example 10:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

A suspension of 0.9 g ($2.3 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-4-chloro-5-chloromethyl-1H-imidazol-1-yl)-methyl]benzoate hydrochloride in 4.5 ml of methyl anthranilate is heated at 120°C for 20 minutes. After the addition of 15 ml of water and 15 ml of a saturated solution of sodium bicarbonate, the reaction mixture is extracted with 30 ml of ethyl acetate. The organic phase is washed with water until the washings are neutral, dried over magnesium sulfate and evaporated under reduced pressure. The yellow oil obtained is purified by chromatography on silica using a toluene/ethyl acetate mixture (90/10; v/v) as the eluent to give 1.07 g (yield: 90%) of a colorless oil.
^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.86 (t, 3H); 1.34 (m, 2H); 1.66 (m, 2H); 2.52 (t, 3H); 3.76 (s, 3H); 3.91 (s, 3H); 4.21 (d, 2H); 5.30 (s, 2H); 6.62 (t, 1H); 6.72 (d, 1H); 6.93 (d, 2H); 7.31 - 7.39 (m, 1H); 7.69 (m, 1H); 7.81 (d, 1H); 7.90 (d, 1H).

The product of Example 56 and the following product were obtained by a procedure analogous to the preparation of Example 10:

Example 57:

Methyl 4-[[2-butyl-4-chloro-5-[((4-cyanophenyl)amino)-methyl]-1H-imidazol-1-yl]methyl]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.87 (t, 3H); 1.35 (m, 2H); 1.67 (m, 2H); 2.55 (t, 2H); 3.91 (s, 3H); 4.18 (d, 2H); 4.45 (t, 1H); 5.21 (s, 2H); 6.68 - 6.76 (m, 2H); 6.95 (d, 2H); 7.33 - 7.40 (m, 2H); 7.94 (d, 2H).

Example 11:

Ethyl N-[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]indole-2-carboxylate

0.68 g ($22.6 \cdot 10^{-3}$ mol) of 80% sodium hydride in oil is added in portions to a solution of 4.26 g ($22.5 \cdot 10^{-3}$ mol) of ethyl indole-2-carboxylate in 50 ml of anhydrous dimethylformamide. After stirring at room temperature for 20 minutes, 4 g ($11.26 \cdot 10^{-3}$ mol) of methyl 4-[(2-butyl-4-chloro-5-chloromethyl-1H-imidazol-1-yl)methyl]benzoate hydrochloride are added. Stirring is maintained for 4.5 hours. 400 ml of water are added to the reaction mixture and several extractions are carried out with ethyl acetate. The organic phases are washed with water until the washings are neutral, dried over magnesium sulfate and evaporated under reduced pressure. The brown oil obtained is purified by chromatography on silica using a toluene/ethyl acetate mixture (95/5; v/v) as the eluent to give 2.06 g (yield: 36%) of the expected product.

M.p. = 136°C

The product of Example 12 was prepared by an analogous procedure.

Example 13:

Methyl 2-[[[4-chloro-2-propyl-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

2.93 g ($7.7 \cdot 10^{-3}$ mol) of methyl 4-[(4-chloro-5-chloromethyl-2-propyl-1H-imidazol-1-yl)methyl]benzoate hydrochloride are suspended in 30 ml of anhydrous toluene. 2.6 g ($17 \cdot 10^{-3}$ mol) of methyl anthranilate are added and the mixture is then refluxed for 3 hours, with stirring. The reaction mixture is then poured into a saturated solution of sodium bicarbonate. Extraction is carried out with ethyl acetate. The organic phases are washed with water until the washings are neutral, dried over magnesium sulfate and concentrated. The oily residue obtained is purified by chromatography on silica using a toluene/ethyl acetate mixture (95/5; v/v) as the eluent to give 2.1 g (yield: 59%) of a beige solid.

M.p. = 108°C

The products of Examples 14, 15, 17, 18, 21 and 22 and the following products were prepared by an analogous procedure:

Example 16:

Methyl 3-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]naphthalene-2-carboxylate

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 1.33 (m, 2H); 1.67 (m, 2H); 2.51 (t, 3H); 3.83 (s, 3H); 3.92 (s, 3H); 4.30 (d, 2H); 5.29 (s, 1H); 6.90 (m, 3H); 7.20 (m, 1H); 7.39 (m, 2H); 7.58 (d, 1H); 7.66 (d, 1H); 7.84 (d, 2H); 8.41 (s, 1H).

Example 19:

Methyl 2-[[[2-butyl-4-iodo-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.85 (t, 3H); 1.28 (m, 2H); 1.68 (m, 2H); 2.55 (t, 2H); 3.77 (s, 3H); 3.91 (s, 3H); 4.18 (d, 2H); 5.23 (s, 2H); 6.64 (m, 2H); 6.89 (d, 2H); 7.33 (t, 1H); 7.66 (t, 1H); 7.80 (d, 1H); 7.88 (d, 2H).

Example 20:

Methyl 2-[[[2-butyl-4-trifluoromethyl-1-[(4-(methoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

Colorless oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.34 (m, 2H); 1.71 (m, 2H); 2.59 (t, 2H); 3.78 (s, 3H); 3.91 (s, 3H); 4.32 (d, 2H); 5.22 (s, 2H); 6.64 (m, 2H); 6.92 (d, 2H); 7.31 (m, 1H); 7.64 (t, 1H); 7.83 (d, 1H); 7.92 (d, 2H).

Example 215:

Methyl 4-[[2-butyl-5-[((2-(((3-(dimethylamino)propyl)-amino)carbonyl)phenyl)amino)methyl]-1H-imidazol-1-yl]-methyl]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.86 (t, 3H); 1.32 (m, 2H); 1.70 (m, 4H); 2.27 (s, 6H); 2.48 (m, 4H); 3.44 (m, 2H); 3.88 (s, 3H); 4.12 (d, 2H); 5.21 (s, 2H); 6.59 (t, 1H); 6.64 (d, 1H); 6.94 (d, 2H); 7.0 (s, 1H); 7.23 (t, 2H); 7.91 (d, 2H); 7.99 (t, 1H); 8.27 (t, 1H).

Example 23:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-carboxyphenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

0.8 g ($20 \cdot 10^{-3}$ mol) of sodium hydroxide and 10 ml of water are added to a solution of 9 g ($19.1 \cdot 10^{-3}$ mol) of methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxy-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate in 80 ml of methanol. The reaction mixture is heated at 50°C for 3.5 hours. The methanol is evaporated off under reduced pressure and the residue is diluted with 150 ml of water. The aqueous phase is washed with 3 times 50 ml of ethyl acetate and then acidified to pH 5 with 1 N hydrochloric acid and extracted with 2 times 50 ml of ethyl acetate. The organic phases are washed with water until the washings are neutral, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The solid residue is purified by chromatography on silica using a dichloromethane/methanol mixture (95/5; v/v) as the eluent to give 5.1 g (yield: 58%) of a white solid.

M.p. = 181°C

The products of Examples 24, 223 and 224 were obtained by an analogous procedure.

Example 25:

Phenylmethyl 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

A solution of 2.6 g ($4.7 \cdot 10^{-3}$ mol) of phenyl-methyl 2-[[[2-butyl-1-[(4-(1,1-dimethylethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate in 10 ml of trifluoroacetic acid is stirred at 0°C for 3 hours. The trifluoroacetic acid is evaporated off under reduced pressure. After the addition of 60 ml of

water to the residue and of sodium hydroxide to pH 6, extraction is carried out with 2 times 30 ml of ethyl acetate. The organic phase is washed with 2 times 10 ml of water, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give 2.4 g (yield: 100%) of a yellow foam.

M.p. = 90°C

The products of Examples 195 to 197 were prepared by an analogous procedure.

Example 26:

2,2-Dimethyl-1,3-dioxolan-4-ylmethyl 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]-amino]benzoate

0.39 g of 10% palladium-on-charcoal is added under a nitrogen atmosphere to a solution of 3.9 g ($6.38 \cdot 10^{-3}$ mol) of 2,2-dimethyl-1,3-dioxolan-4-ylmethyl 2-[[[2-butyl-1-[((4-phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate in 150 ml of methanol. The reaction medium is then placed under a hydrogen atmosphere and stirred for 2.5 hours. After filtration, the methanol is evaporated off under reduced pressure. The residue obtained is purified by chromatography on silica using a dichloromethane/methanol mixture (90/10; v/v) as the eluent to give 2.3 g (yield: 69%) of a white foam.

M.p. = 92°C

The products of Examples 27 and 134 to 179 were prepared by an analogous procedure.

Example 28:

2,3-Dihydroxypropyl 2-[[[2-butyl-1-[(4-carboxyphenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

A suspension of 2 g ($3.83 \cdot 10^{-3}$ mol) of 2,2-dimethyl-1,3-dioxolan-4-ylmethyl 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate in 100 ml of 1 N hydrochloric acid is stirred at room temperature for 2 hours. The reaction mixture is brought to pH 7 with a 5 N solution of sodium hydroxide and then extracted with 2 times 50 ml of butanol. The organic phase is washed with water and evaporated under reduced pressure. The white foam obtained is purified by chromatography on silica using a methylene chloride/methanol mixture (90/10; v/v) as the eluent to give 7.3 g (yield: 71%) of a white powder.

M.p. = 123°C

The products of Examples 29, 30, 31, 71 and 218 were prepared by an analogous procedure.

Example 32:

2-[[[2-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid

5.1 g ($11.7 \cdot 10^{-3}$ mol) of methyl 2-[[[2-butyl-1-[((4-methoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate are dissolved in 50 ml of methanol. 17.6 ml ($35.2 \cdot 10^{-3}$ mol) of 2 N sodium hydroxide are added, the mixture is refluxed for 4 hours, the methanol is then evaporated off and the residue is solubilized in iced water. The diacid is precipitated by the addition of 1 N hydrochloric acid until the pH is 4. The solid obtained is filtered off, washed with water until the washings are neutral, and dried over

phosphorus pentoxide to give 3.75 g of a pale yellow solid. This crude product is washed with hot methanol to give 3.5 g (yield: 73.5%) of a white solid.

M.p. = 234°C

The products of Examples 33 to 52, 55, 66, 67, 198 to 212, 226 and 228 were prepared by an analogous procedure.

Example 53:

Dipotassium salt of 2-[[[2-butyl-1-[(4-carboxyphenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid

203 mg ($0.5 \cdot 10^{-3}$ mol) of 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoic acid are mixed with 10 ml of 0.1 N potassium hydroxide (10^{-3} mol) and 20 ml of water. The mixture is stirred until a clear solution is obtained, and lyophilized to give 240 mg (yield: 100%) of a white solid.

M.p. = 206°C

Example 54:

Methyl N-[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]-N-(methyl-carbonyl)-2-aminobenzoate

12.5 ml of acetic anhydride are added to a solution of 2.5 g ($5.31 \cdot 10^{-3}$ mol) of methyl 2-[[[2-butyl-4-chloro-1-[(4-(methoxycarbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate in 25 ml of pyridine and the mixture is heated at 60°C for 1.5 hours. The solution is poured into a cold 1 N solution of hydrochloric acid. Extraction is carried out with ethyl acetate and the organic phases are washed with a 1 N solution of hydrochloric acid and then with brine

until the pH is 4. After drying over magnesium sulfate and concentration, 3.3 g of a pale yellow oil are obtained which is crystallized from 100 ml of ethyl ether to give 1.85 g (yield: 73%) of white crystals.

M.p. = 142°C

Example 58:

Methyl 2-[[[2-butyl-4-chloro-1-[(4-((triphenylmethyl)-1H-tetrazol-5-yl)phenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate

4.3 g ($9.84 \cdot 10^{-3}$ mol) of methyl 2-[[[2-butyl-4-chloro-1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate are suspended in 80 ml of anhydrous toluene. 830 mg ($12.7 \cdot 10^{-3}$ mol) of sodium azide and 2.94 g ($14.7 \cdot 10^{-3}$ mol) of trimethyltin chloride are added and the mixture is then refluxed for 48 hours. After cooling to room temperature, 1.19 g ($11.8 \cdot 10^{-3}$ mol) of triethylamine and 4.11 g ($14.7 \cdot 10^{-3}$ mol) of triphenylmethyl chloride are added. The mixture is stirred at the same temperature for 4 hours, water is then added and extraction is carried out with ethyl acetate. The residue obtained after washing, drying and evaporation is purified by chromatography using a toluene/ethyl acetate mixture (9/1; v/v) as the eluent to give 5.6 g (yield: 79%) of a colorless oil.

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.37 (m, 2H); 1.68 (m, 2H); 2.55 (t, 2H); 3.66 (s, 3H); 4.20 (d, 2H); 5.18 (s, 2H); 6.53 (t, 1H); 6.68 (d, 1H); 6.91 (d, 2H); 7.14 - 7.40 (m, 15H); 7.69 - 7.72 (m, 2H); 7.95 (d, 2H).

The product of Example 59 and the following product were prepared by an analogous procedure:

Example 217:

Pentyl 2-[[[2-butyl-1-[(4-((triphenylmethyl)-1H-tetrazol-5-yl)phenyl)methyl]-1H-imidazol-5-yl]methyl]-amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.88 (m, 6H); 1.23 - 1.39 (m, 8H); 1.65 - 1.71 (m, 2H); 2.58 (t, 2H); 4.10 (d, 2H); 4.16 (t, 2H); 5.18 (s, 2H); 6.58 (t, 1H); 6.63 (d, 1H); 6.94 (d, 2H); 7.02 (s, 1H); 7.13 - 7.38 (m, 16H); 7.75 (t, 1H); 7.82 (d, 1H); 8.01 (d, 2H).

Example 60:

Methyl 2-[[[2-butyl-1-[(4-((((2-methylphenyl)sulfonyl)-amino)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]-amino]benzoate

0.6 g ($3.49 \cdot 10^{-3}$ mol) of orthotoluenesulfonamide, 0.67 g ($3.49 \cdot 10^{-3}$ mol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.43 g ($3.49 \cdot 10^{-3}$ mol) of dimethylaminopyridine are added to a suspension of 1.47 g ($3.49 \cdot 10^{-3}$ mol) of methyl 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-methyl]amino]benzoate in 50 ml of dichloromethane. After stirring for 20 hours at room temperature, the solvent is evaporated off under reduced pressure. The residue obtained is purified by chromatography on silica using a toluene/isopropanol mixture (80/20; v/v) as the eluent to give 1.6 g (yield: 80%) of a white solid.

M.p. = 135°C

The products of Examples 61, 64, 187 to 194 and 227 and the following products were prepared by an analogous procedure:

Example 62:

Phenylmethyl 2-[[[2-butyl-1-[(4-((2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

Yellowish oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.34 (m, 2H); 1.37 (s, 3H); 1.44 (s, 3H); 1.70 (m, 2H); 2.56 (t, 2H); 3.83 (m, 1H); 4.10 (m, 1H); 4.19 (d, 2H); 4.32 (m, 2H); 4.41 (m, 1H); 5.18 (s, 2H); 5.22 (s, 2H); 6.64 (m, 2H); 6.91 (d, 2H); 7.05 (s, 1H); 7.28 - 7.41 (m, 6H); 7.7 (t, 1H); 7.92 (m, 3H).

Example 63:

2-(Morpholin-1-yl)ethyl 2-[[[2-butyl-1-[(4-((2-(morpholin-1-yl)ethoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

Colorless oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.34 (m, 2H); 1.69 (m, 2H); 2.56 (m, 10H); 2.73 (m, 4H); 3.71 (m, 8H); 4.19 (d, 2H); 4.32 (t, 2H); 4.44 (t, 2H); 5.19 (s, 2H); 6.64 (q, 2H); 6.95 (d, 2H); 7.04 (s, 1H); 7.31 (m, 1H); 7.70 (t, 1H); 7.82 (d, 1H); 7.92 (d, 2H).

Example 65:

2,2-Dimethyl-1,3-dioxolan-4-ylmethyl 2-[[[2-butyl-1-[(4-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxycarbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.29 (m, 2H); 1.38 (s, 6H); 1.41 (s, 6H); 1.69 (m, 2H); 2.56 (t, 2H); 3.85 (m, 2H); 4.10 - 4.25 (m, 6H); 4.35 - 4.47 (m, 4H); 5.19 (s, 2H); 8.61 (m,

2H); 6.95 (d, 2H); 7.04 (s, 1H); 7.34 (m, 1H); 7.65 (t, 1H); 7.86 (d, 1H); 7.95 (d, 2H).

Example 68:

((Diethylamino)carbonyl)methyl 2-[[[2-butyl-1-[(4-((((diethylamino)carbonyl)methoxy)carbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

1.09 g ($10.8 \cdot 10^{-3}$ mol) of triethylamine, 147 mg (10^{-3} mol) of sodium iodide and 1.46 g ($9.8 \cdot 10^{-3}$ mol) of N,N-diethylchloroacetamide are added to a suspension of 2 g ($4.9 \cdot 10^{-3}$ mol) of 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid in 5 ml of dimethylformamide. The mixture is heated at 90°C for 2 hours. After cooling, water is added and extraction is carried out with ethyl acetate. The organic phases are washed with water, dried over magnesium sulfate and concentrated. The crude product obtained is purified by chromatography on silica using a toluene/isopropyl alcohol mixture (9/1; v/v) as the eluent. After evaporation, 1.1 g (yield: 35%) of the expected product are obtained.

M.p. = 55°C

The products of Examples 180 to 183 and the following products were prepared by an analogous procedure:

Example 69:

(((1,1-Dimethylethyl)carbonyl)oxy)methyl 2-[[[2-butyl-1-[(4-(((((1,1-dimethylethyl)carbonyl)oxy)methoxy)-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

Yellow oil

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.88 (t, 3H); 1.21 (s, 9H); 1.22 (s, 9H); 1.37 (m, 2H); 1.70 (m, 2H); 2.56 (t, 2H); 4.19 (d, 2H); 5.19 (s, 2H); 5.88 (s, 2H); 5.98 (s, 2H); 6.64 (m, 2H); 6.95 (d, 2H); 7.05 (s, 1H); 7.35 (t, 1H); 7.60 (t, 1H); 7.86 (d, 1H); 7.95 (d, 2H).

Example 70:

((4-Methylpiperazin-1-yl)carbonyl)methyl 2-[[[2-butyl-1-[(4-((((4-methylpiperazin-1-yl)carbonyl)methoxy)-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (t, 3H); 1.26 (m, 2H); 1.70 (m, 2H); 2.33 (s, 6H); 2.43 (m, 8H); 2.54 (t, 2H); 3.46 (m, 4H); 3.63 (m, 4H); 4.29 (d, 2H); 4.86 (s, 2H); 4.95 (s, 2H); 5.18 (s, 2H); 6.89 (d, 2H); 7.11 (s, 1H); 7.39 (d, 1H); 7.51 (s, 1H); 7.82 (t, 1H); 7.96 (d, 2H); 8.06 (d, 1H).

Example 184:

[2-[[[2-Butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenylcarbonyl-oxy]methyl butanoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.87 (m, 6H); 1.31 (m, 2H); 1.67 (m, 4H); 2.33 (t, 2H); 2.59 (t, 2H); 4.19 (d, 2H); 5.18 (s, 2H); 5.35 (s, 2H); 5.88 (s, 2H); 6.59 (m, 2H); 6.90 (d, 2H); 7.04 (s, 1H); 7.30 - 7.50 (m, 6H); 7.59 (t, 1H); 7.82 - 7.96 (m, 3H).

Example 185:

((Propylcarbonyl)oxy)methyl 2-[[[2-butyl-1-[(4-((((propylcarbonyl)oxy)methoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.93 (m, 9H); 1.34 (m, 2H); 1.63 (m, 6H); 2.36 (m, 4H); 2.56 (t, 2H); 4.19 (d, 2H); 5.18 (s, 2H); 5.88 (s, 2H); 5.96 (s, 2H); 6.61 (m, 2H); 6.92 (d, 2H); 7.04 (s, 1H); 7.35 (m, 1H); 7.58 (t, 1H); 7.86 (m, 1H); 7.95 (d, 2H).

Example 186:

Ethyl 2-[[[2-[[[2-butyl-1-[(4-(methoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]phenyl]carbonyl-oxy]acetate

^{1}H NMR (300 MHz; $CDCl_3$; ppm)
0.85 (t, 3H); 1.29 (t, 3H); 1.36 (m, 2H); 1.69 (m, 2H); 2.56 (t, 2H); 3.91 (s, 3H); 4.17 (d, 2H); 4.26 (m, 2H); 4.71 (s, 2H); 5.17 (s, 2H); 6.65 (m, 2H); 6.94 (d, 2H); 7.04 (s, 1H); 7.33 (m, 1H); 7.53 (t, 1H); 7.95 (m, 3H).

Example 72:

((4-Methylpiperazin-1-yl)carbonyl)methyl 2-[[[2-butyl-1-[(4-((((4-methylpiperazin-1-yl)carbonyl)methoxy)-carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-4-nitrobenzoate trihydrochloride

1.4 g ($1.9 \cdot 10^{-3}$ mol) of ((4-methylpiperazin-1-yl)carbonyl)methyl 2-[[[2-butyl-1-[(4-((((4-methylpiperazin-1-yl)carbonyl)methoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]-4-nitrobenzoate are dissolved in a mixture of 25 ml of ethyl acetate and 10 ml of methylene chloride. An excess of ethyl ether saturated with gaseous hydrogen chloride is added. A yellow gum precipitates. After decantation, this is washed with ethyl ether and dried to give 1.4 g (yield: 87%) of a yellow powder.

M.p. = 194°C

The product of Example 213 was prepared by an

analogous procedure.

Example 73:

2-(Morpholin-1-yl)ethyl 2-[[[2-butyl-1-[(4-((2-morpholin-1-yl)ethoxy)carbonyl)phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate trioxalate

A solution of 0.302 g ($3.36 \cdot 10^{-3}$ mol) of oxalic acid in a mixture of 1 ml of methanol and 5 ml of ethyl acetate is added at room temperature to a solution of 0.71 g ($1.12 \cdot 10^{-3}$ mol) of 2-(morpholin-1-yl)ethyl 2-[[[2-butyl-1-[(4-((2-morpholin-1-yl)ethoxy)carbonyl)-phenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoate in 15 ml of ethyl acetate. The reaction mixture is stirred for 1 hour and the precipitate formed is filtered off and dried under vacuum. The solid obtained is dissolved in 20 ml of water and lyophilized to give 0.7 g (yield: 69%) of a yellowish foam.

M.p. = 102°C

Example 214:

Pentyl 2-[[[2-butyl-1-[(4-(pentoxycarbonyl)phenyl)-methyl]-1H-imidazol-5-yl]methyl]amino]benzoate

650 mg (0.052 mol) of 4-dimethylaminopyridine, 1 g (0.052 mol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and 458 mg (0.052 mol) of n-pentanol are added to a suspension of 1.07 g (0.0026 mol) of 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid in 25 ml of dichloromethane. The reaction mixture is stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue is purified by flash chromatography on silica using a methylcyclohexane/acetone mixture (85/15; v/v) as the eluent to give

1.2 g of a yellowish oil (yield: 83%).

^{1}H NMR (300 MHz; $CDCl_3$; ppm)

0.92 (m, 9H); 1.37 (m, 10H); 1.67 (m, 6H); 2.55 (t, 2H); 4.18 (m, 4H); 4.29 (t, 2H); 5.19 (s, 2H); 6.61 (q, 2H); 6.93 (d, 2H); 7.04 (s, 1H); 7.30 (m, 1H); 7.83 (t, 1H); 7.73 - 7.93 (m, 3H).

Example 216:

Methyl 4-[[2-butyl-5-[((2-(((3-(dimethylamino)propyl)-amino)carbonyl)phenyl)amino)methyl]-1H-imidazol-1-yl]-methyl]benzoate fumarate

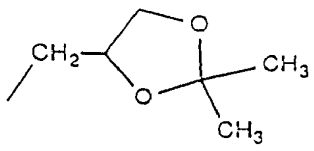
0.96 g ($1.9 \cdot 10^{-3}$ mol) of methyl 4-[[2-butyl-5-[((2-(((3-(dimethylamino)propyl)amino)carbonyl)phenyl)-amino)methyl]-1H-imidazol-1-yl]methyl]benzoate is dissolved in 30 ml of ethyl acetate. The solution is heated to 50°C and a solution of 0.214 g ($1.85 \cdot 10^{-3}$ mol) of fumaric acid in 4 ml of methanol is added. After cooling to 15°C over 1 hour, the precipitate obtained is filtered off. After drying, 1 g (yield: 87%) of the expected product is obtained.

M.p. = 164°C

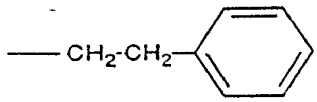
A number of compounds according to the invention have been collated in Tables I to VII below. The symbols used in these Tables have the following meanings:

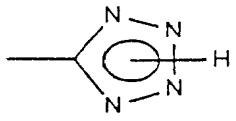
Et = $-C_2H_5$
n-Pr = $-CH_2-CH_2-CH_3$
i-Pr = $-CH(CH_3)_2$
c-Pr = cyclopropyl
n-Bu = $-CH_2-CH_2-CH_2-CH_3$
s-Bu = $-CH(CH_3)-CH_2-CH_3$
i-Bu = $-CH_2-CH(CH_3)_2$

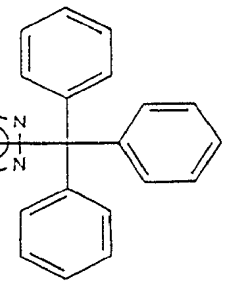
t-Bu = $-C(CH_3)_3$
n-Pent = $-(CH_2)_4-CH_3$
i-Pent = $-CH_2-CH_2-CH(CH_3)_2$
c-Pent = cyclopentyl
n-Hex = $-(CH_2)_5-CH_3$
c-Hex = cyclohexyl
n-Hep = $-(CH_2)_6-CH_3$
n-Dec = $-(CH_2)_9-CH_3$
n-Cet = $-(CH_2)_{15}-CH_3$
Mcs = $-CH_2-CH_2-O-CH_3$
Deae = $-CH_2-CH_2-N(C_2H_5)_2$
Gl = $-CH_2-CH(OH)-CH_2OH$

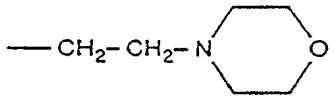
Ig = 

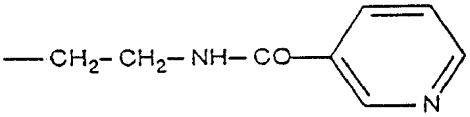
Ph = phenyl
Bn = benzyl

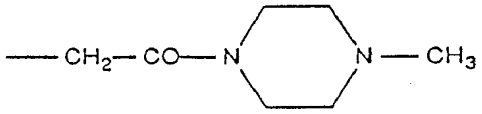
Eph = 

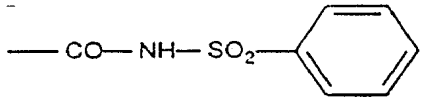
TT = 

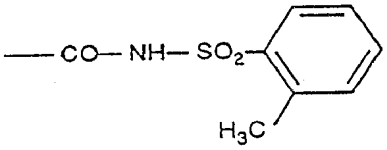
TTT = 

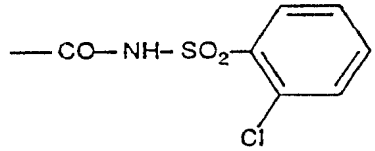
MOE = 

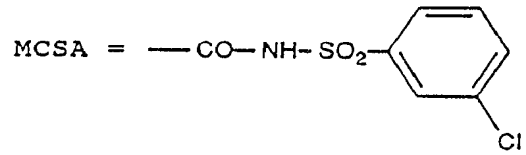
NAE = 

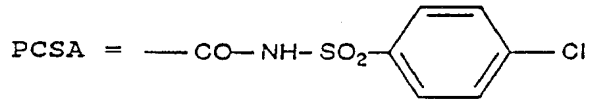
Pz = 

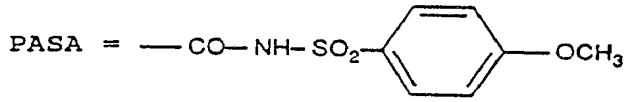
PhSA = 

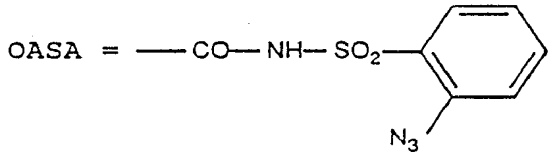
TSA = 

OCSA = 

MCSA = 

PCSA = 

PASA = 

OASA = 

MESA = $-CO-NH-SO_2-CH_3$

AAE = $-CH_2-CO-N(CH_2-CH_3)_2$

AAP = $-CH_2-CO-N(CH_2-CH_2-CH_3)_2$

AAHE = $-CH_2-CO-N(CH_2-CH_2OH)_2$

AAMHE = $-CH_2-CO-N(CH_3)(CH_2-CH_2OH)$

APE = $-CH(CH_3)-CO-N(CH_2-CH_3)_2$

W = $-CH_2-CO_2-$

X = $-CH(CH_3)-CO_2-$

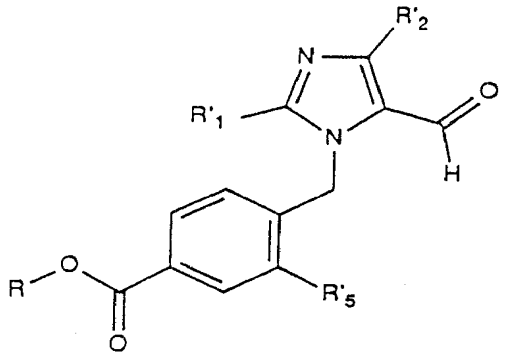
Y = $-CH_2-O-CO-$

Z = $-CH(CH_3)-O-CO-$

Gly = $-NH-CH_2-CO-$

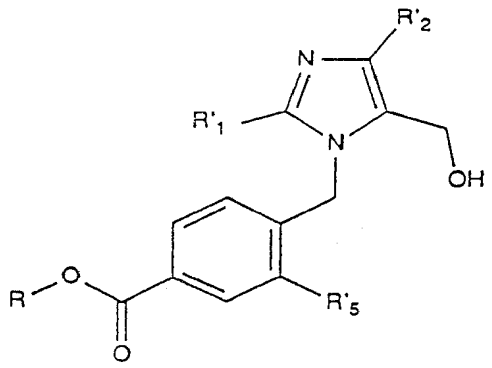
L-Val = $-NH-CH[CH(CH_3)_2]-CO-$ (L)

TABLE A



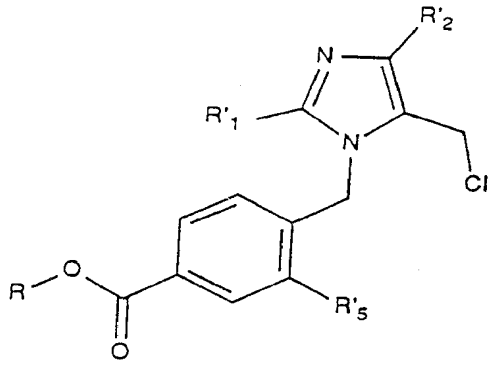
Prep	R'$_1$	R'$_2$	R'$_5$	R	M.p.(°C)
2	n-Pr	Cl	H	CH_3	89
3	n-Pr	H	H	CH_3	72
4	n-Bu	CF_3	H	CH_3	59
5	n-Bu	H	H	H	148
6	n-Bu	H	H	Bn	-
9	n-Bu	Cl	H	t-Bu	54
10	n-Bu	Cl	Cl	CH_3	112
11	n-Bu	I	H	CH_3	82
12	n-Bu	H	H	t-Bu	-
31	n-Bu	Cl	H	Et	60
32	n-Bu	H	H	Et	-
33	n-Bu	Cl	H	H	126
34	n-Bu	H	H	n-Cet	56
35	n-Bu	H	H	n-Pent	-
36	n-Bu	H	H	n-Bu	-
37	n-Bu	H	H	i-Bu	-
38	n-Bu	H	H	CH_2-c-Pr	-
39	n-Bu	H	H	i-Pent	-
40	n-Bu	Cl	H	Bn	-
62	n-Bu	S-CH_3	H	CH3	72-74

TABLE B



Prep	R'1	R'2	R'5	R	M.p.(°C)
7	n-Bu	H	H	CH_3	144
13	n-Bu	CF_3	H	CH_3	113
14	n-Bu	Cl	Cl	CH_3	108
15	n-Pr	Cl	H	CH_3	120
16	n-Bu	H	H	t-Bu	163
17	n-Bu	H	H	Bn	111
18	n-Bu	I	H	CH_3	150
19	n-Bu	Cl	H	t-Bu	174
20	n-Bu	Cl	H	CH_3	94
21	n-Pr	H	H	CH_3	135
41	n-Bu	S-CH_3	H	CH_3	154
42	n-Bu	H	H	n-Pent	137
43	n-Bu	H	H	Et	140
44	n-Bu	H	H	n-Bu	140
45	n-Bu	H	H	n-Cet	75
46	n-Bu	H	H	i-Bu	144
47	n-Bu	H	H	CH_2-c-Pr	100
48	n-Bu	H	H	i-Pent	170
49	n-Bu	Cl	H	Bn	127

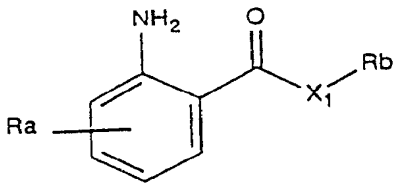
TABLE C



Prep	R'1	R'2	R'5	R	M.p.(°C)
8*	n-Bu	H	H	CH_3	158
22	n-Pr	Cl	H	CH_3	128
23	n-Bu	H	H	Bn	160
24	n-Bu	H	H	t-Bu	150-191
25	n-Bu	Cl	Cl	CH_3	70
26	n-Bu	I	H	CH_3	140
27*	n-Bu	Cl	H	t-Bu	133
28*	n-Bu	Cl	H	CH_3	120
29*	n-Pr	H	H	CH_3	172
30	n-Bu	CF_3	H	CH_3	-
51*	n-Bu	S-CH_3	H	CH_3	115
53*	n-Bu	H	H	n-Pent	130
54*	n-Bu	H	H	Et	130
55*	n-Bu	H	H	n-Bu	130
56*	n-Bu	H	H	n-Cet	135
57*	n-Bu	H	H	i-Bu	148
58*	n-Bu	H	H	CH_2-c-Pr	150
59*	n-Bu	H	H	i-Pent	135
61	n-Bu	Cl	H	Bn	-

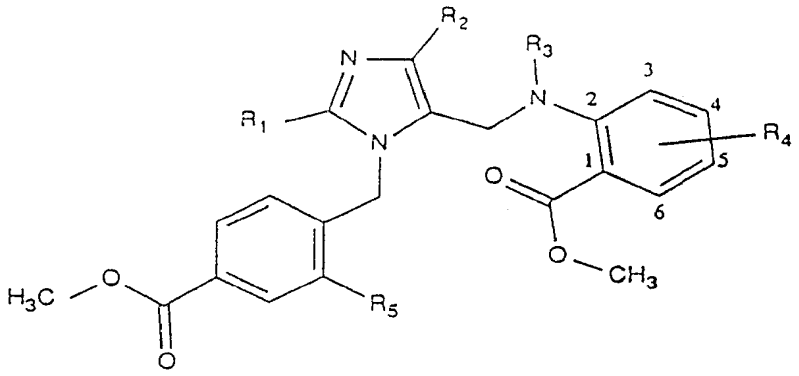
Note: * hydrochlorides

TABLE D



Prep	R_a	X_1	R_b	M.p.(°C)
64	H	O	AAP	64
65	H	O	$CH(CH_3)(CO)Et$	-
66	H	O	W-Et	-
67	H	O	W-n-Pent	-
68	H	O	CH_2-c-Pr	-
69	H	O	CH_2-CO-Et	53
70	H	O	$CH(CH_3)$-n-Bu	-
71	H	O	Deae	-
72	H	O	APE	134
73	H	O	AAHE	107
74	H	O	AAMHE	103
75	H	O	Z-t-Bu	80
76	H	O	$Z\text{-}CH(Et)_2$	-
77	H	O	Z-c-Pent	-
78	H	O	Z-c-Hex	-
79	H	O	Y-n-Pent	-
80	H	O	Z-n-Pent	-
81	H	O	$Z\text{-}CH_2$-c-Hex	-
82	H	O	$Z\text{-}CH_2$-c-Pent	-
83	H	O	Y-t-Bu	-
84	H	NH	$(CH_2)_3\text{-}N(CH_3)_2$	76
85	H	NH	AAE	62
86	H	NH	$CH(iPr)\text{-}CO_2Et$	-
87	6-CH_3	O	n-Pent	-
88	6-Cl	O	n-Pent	-

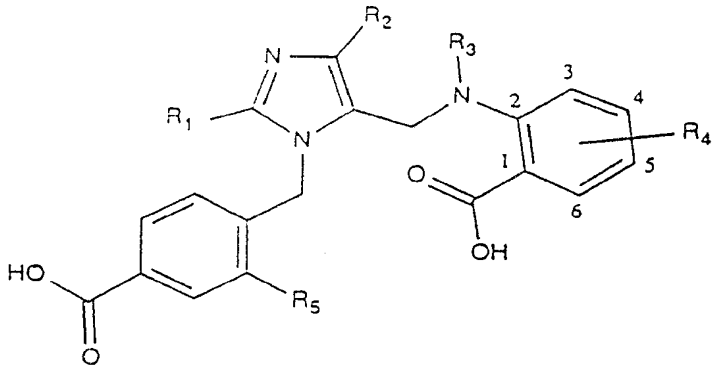
TABLE I



Ex	R_1	R_2	R_3	R_4	R_5	M.p.(°C)
1	n-Bu	H	H	H	H	-
2	n-Bu	H	H	4-NO_2	H	144
3	n-Pr	H	H	H	H	-
6	n-Bu	Cl	H	3,5-diCl	H	-
7	n-Bu	Cl	H	3-CH_3	H	-
8	n-Bu	Cl	CH_3	H	H	-
9	n-Bu	Cl	H	3,4,5-tri OCH_3	H	-
10	n-Bu	Cl	H	H	H	-
13	n-Pr	Cl	H	H	H	108
14	n-Bu	Cl	H	5-Cl	H	90
15	n-Bu	Cl	H	4-Cl	H	116
17	n-Bu	Cl	H	4-NO_2	H	136
18	n-Bu	Cl	H	5-CH_3	H	*
19	n-Bu	I	H	H	H	-
20	n-Bu	CF_3	H	H	H	-
21	n-Bu	Cl	H	H	Cl	140
54	n-Bu	Cl	$COCH_3$	H	H	142
75	n-Bu	SCH_3	H	H	H	-
116	n-Pr	H	H	4-NO_2	H	-
225	n-Bu	H	H	4-N_3	H	132

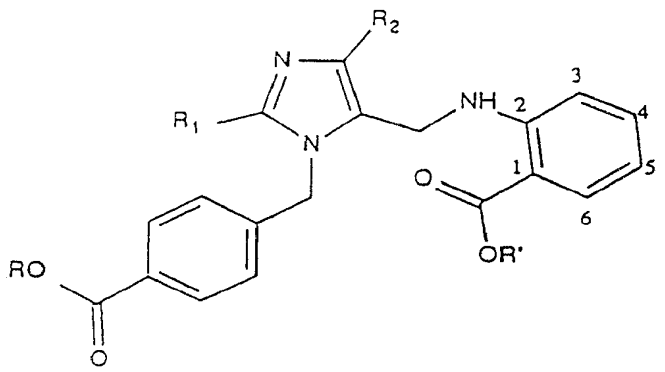
Note: * double melting point: 87°C, then 97°C

TABLE II



Ex	R_1	R_2	R_3	R_4	R_5	M.p.(°C)
32	n-Bu	H	H	H	H	234
35	n-Bu	H	H	4-NO_2	H	250
36	n-Pr	H	H	H	H	249
37	n-Bu	Cl	H	3-CH_3	H	115
38	n-Bu	Cl	CH_3	H	H	147
39	n-Bu	Cl	H	3,5-diCl	H	220
40	n-Bu	Cl	H	3,4,5-tri OCH_3	H	212
41	n-Bu	Cl	H	H	Cl	244
42	n-Pr	Cl	H	H	H	246
43	n-Bu	CF_3	H	H	H	262
44	n-Bu	I	H	H	H	225
45	n-Bu	Cl	H	5-CH_3	H	232
46	n-Bu	Cl	H	4-NO_2	H	260
48	n-Bu	Cl	H	4-Cl	H	247
49	n-Bu	Cl	H	5-Cl	H	248
50	n-Bu	Cl	H	H	H	235
55	n-Bu	Cl	$COCH_3$	H	H	230
198	n-Bu	SCH_3	H	H	H	207
199	n-Bu	H	H	6-CH_3	H	225
200	n-Bu	H	H	6-Cl	H	259
212	n-Pr	H	H	4-NO_2	H	281
226	n-Bu	H	H	4-N_3	H	215(dec)

TABLE III



Ex	R_1	R_2	R	R'	M.p.(°C)
4	n-Bu	H	Bn	Ig	-
5	n-Bu	H	t-Bu	Bn	-
22	n-Bu	Cl	t-Bu	CH_3	102
23	n-Bu	Cl	H	CH_3	181
24	n-Bu	H	H	CH_3	85
25	n-Bu	H	H	Bn	90
26	n-Bu	H	H	Ig	92
27	n-Bu	H	Ig	H	202
28	n-Bu	H	H	Gl	123
29	n-Bu	H	Gl	H	134
53	n-Bu	H	K	K	206
62	n-Bu	H	Ig	Bn	-
63	n-Bu	H	MOE	MOE	-
64	n-Bu	H	NAE	NAE	84
65	n-Bu	H	Ig	Ig	-
68	n-Bu	H	AAE	AAE	55
69	n-Bu	H	Y-t-Bu	Y-t-Bu	-
70	n-Bu	H	Pz	Pz	-
71	n-Bu	H	Gl	Gl	60
73**	n-Bu	H	MOE	MOE	102

TABLE III (continuation 1)

Ex	R_1	R_2	R	R'	M.p.(°C)
74	n-Bu	Cl	Bn	n-Pent	-
76	n-Bu	H	CH_3	AAE	81
77	n-Bu	H	CH_3	AAP	-
78	n-Bu	H	Bn	AAP	-
79	n-Bu	H	Bn	AAE	-
80	n-Bu	H	Bn	APE	-
81	n-Bu	H	Bn	AAHE	-
82	n-Bu	H	Bn	AAMHE	-
84	n-Bu	H	Bn	W-Et	-
85	n-Bu	H	Bn	Z-CH-Et_2	-
86	n-Bu	H	Bn	Z-c-Pent	-
90	n-Bu	H	Bn	Z-CH_2-c-Pent	-
91	n-Bu	H	Bn	Z-c-Hex	-
92	n-Bu	H	Bn	Z-t-Bu	-
93	n-Bu	H	Bn	Y-t-Bu	-
94	n-Bu	H	Bn	Y-n-Pent	-
95	n-Bu	H	Bn	Deae	-
96	n-Bu	H	Bn	$CH(CH_3)$-n-Bu	-
97	n-Bu	H	Bn	$CH(CH_3)$-CO-Et	-
98	n-Bu	H	CH_3	CH_2-CO-Et	100
99	n-Bu	H	Bn	CH_2-CO-Et	-
100	n-Bu	H	Bn	X-Et	-
101	n-Bu	H	Bn	W-n-Pent	-
102	n-Bu	H	Bn	EPh	-
103	n-Bu	H	Bn	Ph	-
104	n-Bu	H	Bn	Mcs	-
105	n-Bu	H	Bn	n-Dec	-
106	n-Bu	H	Bn	n-Hep	-
107	n-Bu	H	Bn	i-Pent	-
108	n-Bu	H	Bn	i-Pr	-
109	n-Bu	H	Bn	CH_2-c-Pr	-
110	n-Bu	H	Bn	i-Bu	-
111	n-Bu	H	Bn	n-Cet	-
112	n-Bu	H	Bn	n-Bu	-
113	n-Bu	H	Et	Et	-
114	n-Bu	H	CH_3	n-Pent	-
115	n-Pr	H	Bn	n-Pent	-
118	n-Bu	H	Bn	Z-n-Pent	-
119	n-Bu	H	Bn	t-Bu	-

TABLE III (continuation 2)

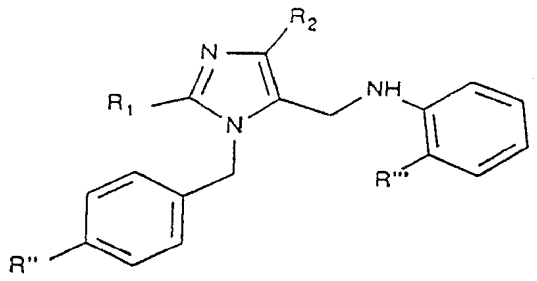
Ex	R_1	R_2	R	R'	M.p.(°C)
120	n-Bu	H	Bn	Et	-
121	n-Bu	H	CH_3	Z-n-Pent	-
122	n-Bu	H	Bn	n-Pent	-
123	n-Bu	H	Bn	Z-CH_2-c-Hex	-
124	n-Bu	H	n-Pent	Bn	-
125	n-Bu	H	CH_3	Bn	-
126	n-Bu	H	Et	Bn	-
127	n-Bu	H	n-Bu	Bn	-
128	n-Bu	H	n-Cet	Bn	-
129	n-Bu	H	i-Bu	Bn	-
130	n-Bu	H	-CH_2-c-Pr	Bn	-
131	n-Bu	H	i-Pent	Bn	-
134	n-Bu	H	H	AAP	140
135	n-Bu	H	H	AAE	168
136	n-Bu	H	H	APE	135
137	n-Bu	H	H	AAHE	108
138	n-Bu	H	H	AAMHE	110
139	n-Bu	H	H	Z-CH-Et_2	170
140	n-Bu	H	H	Z-c-Pent	170
141	n-Bu	H	H	W-Et	155
144	n-Bu	H	H	Z-CH_2-c-Pent	154
145	n-Bu	H	H	Z-c-Hex	60
146	n-Bu	H	H	Z-t-Bu	90
147	n-Bu	H	H	Y-t-Bu	160
148	n-Bu	H	H	Y-n-Pent	140
149	n-Bu	H	H	Y-n-Pr	162
150	n-Bu	H	H	Deae	68
151	n-Bu	H	H	CH(CH_3)-n-Bu	74
152	n-Bu	H	H	CH(CH_3)-CO-Et	80
153	n-Bu	H	H	X-Et	164
154	n-Bu	H	H	W-n-Pent	157
155	n-Bu	H	H	CH_2-CO-Et	144
156	n-Bu	H	H	EPh	128
157	n-Bu	H	H	Ph	231
158	n-Bu	H	H	Mcs	78
159	n-Bu	H	H	n-Dec	50

TABLE III (end)

Ex	R_1	R_2	R	R'	M.p.(°C)
160	n-Bu	H	H	n-Hep	96
161	n-Bu	H	H	i-Pent	164
162	n-Bu	H	H	i-Pr	172
163	n-Bu	H	H	CH_2-c-Pr	171
164	n-Bu	H	H	i-Bu	163
165	n-Bu	H	H	n-Cet	82
166	n-Bu	H	H	n-Bu	151
167	n-Pr	H	H	n-Pent	177
168	n-Bu	H	H	Z-n-Pent	143
169	n-Bu	H	H	Et	173
170	n-Bu	H	H	n-Pent	161
171	n-Bu	H	H	Z-CH_2-c-Hex	114
172	n-Bu	H	n-Pent	H	202
173	n-Bu	H	CH_3	H	188
174	n-Bu	H	Et	H	201
175	n-Bu	H	n-Bu	H	194
176	n-Bu	H	n-Cet	H	152
177	n-Bu	H	i-Bu	H	190
178	n-Bu	H	CH_2-c-Pr	H	198
179	n-Bu	H	i-Pent	H	197
181	n-Bu	H	AAP	AAP	97
182*	n-Bu	H	Pz	Pz	250-260
184	n-Bu	H	Bn	Y-n-Pr	-
185	n-Bu	H	Y-n-Pr	Y-n-Pr	-
186	n-Bu	H	CH_3	W-Et	-
196	n-Bu	H	Bn	H	175
213***	n-Bu	H	H	Deae	206
214	n-Bu	H	n-Pent	n-Pent	-
224	n-Bu	Cl	H	n-Pent	145

Notes : * : 3 HCl
** : 3 HO_2C-CO_2H
*** : 2HCl

TABLE IV



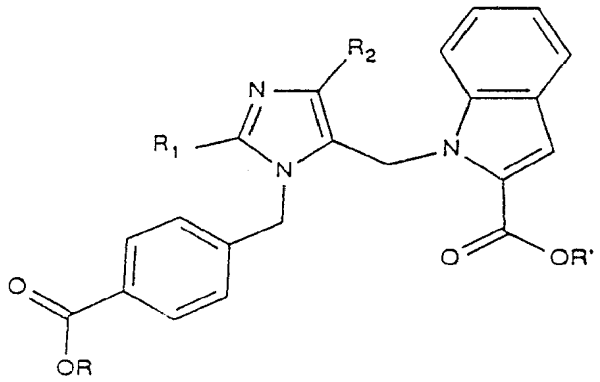
Ex	R_1	R_2	R''	R'''	M.p.(°C)
30	n-Bu	Cl	TT	CO_2CH_3	185
31	n-Bu	Cl	CO_2CH_3	TT	182
51	n-Bu	Cl	TT	CO_2H	158
52	n-Bu	Cl	CO_2H	TT	200
56	n-Bu	Cl	CN	CO_2CH_3	126
57	n-Bu	Cl	CO_2CH_3	CN	-
58	n-Bu	Cl	TTT	CO_2CH_3	-
59	n-Bu	Cl	CO_2CH_3	TTT	130
60	n-Bu	H	TSA	CO_2CH_3	135
61	n-Bu	Cl	TSA	CO_2CH_3	244
66	n-Bu	Cl	TSA	CO_2H	234
67	n-Bu	H	TSA	CO_2H	190
88	n-Bu	H	CO_2CH_3	CONH-AAE	42
89	n-Bu	H	CO_2CH_3	$CONHOCH_3$	146
132	n-Bu	H	4-CN	CO_2-n-Pent	-
142	n-Bu	H	CO_2H	CO-L-Val-OEt	110
143	n-Bu	H	CO_2H	CO-Gly-OEt	140
187	n-Bu	H	TSA	CO_2-Y-n-Pr	228
188	n-Bu	H	OCSA	CO_2CH_3	125
189	n-Bu	H	MCSA	CO_2CH_3	145
190	n-Bu	H	PCSA	CO_2CH_3	220
191	n-Bu	H	PhSA	CO_2CH_3	120
192	n-Bu	H	PASA	CO_2CH_3	228
193	n-Bu	H	MESA	CO_2CH_3	120
194	n-Bu	H	OCSA	CO_2-n-Pent	259

TABLE IV (end)

Ex	R_1	R_2	R''	R'''	M.p.(°C)
201	n-Bu	H	MCSA	CO_2H	235
202	n-Bu	H	PCSA	CO_2H	215
203	n-Bu	H	PhSA	CO_2H	203
204	n-Bu	H	PASA	CO_2H	193
205	n-Bu	H	MESA	CO_2H	238
206	n-Bu	H	CO_2H	$CONH(CH_2)_3N(CH_3)_2$	111
207	n-Bu	H	CO_2H	CONH-AAE	92
208	n-Bu	H	CO_2H	$CONH-O-CH_3$	211
209*	n-Bu	H	CO_2H	$CONH_2$	196
210	n-Bu	H	CO_2H	CONH(n-Bu)	183
211	n-Bu	H	OCSA	CO_2H	198
215	n-Bu	H	CO_2CH_3	$CONH(CH_2)_3N(CH_3)_2$	-
216**	n-Bu	H	CO_2CH_3	$CONH(CH_2)_3N(CH_3)_2$	164
217	n-Bu	H	TTT	CO_2-n-Pent	-
218*	n-Bu	H	TT	CO_2-n-Pent	204
219	n-Bu	H	CO_2CH_3	$CONH_2$	186
220	n-Bu	H	CO_2CH_3	CONH(n-Bu)	125
221	n-Bu	H	CO_2-Bn	CO-L-Val-OEt	-
222	n-Bu	H	CO_2-Bn	CO-Gly-OEt	107
227	n-Bu	H	OASA	CO_2CH_3	150(dec)
228	n-Bu	H	OASA	CO_2H	150(dec)

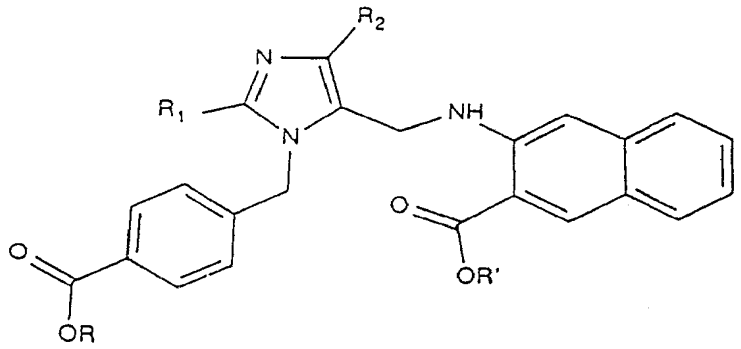
Note :* HCl** fumarate

TABLE V



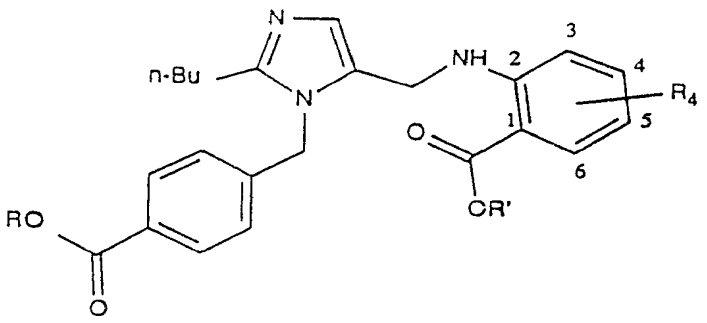
Prep	R_1	R_2	R	R'	M.p.(°C)
11	n-Bu	Cl	CH_3	CH_2CH_3	136
12	n-Bu	H	CH_3	CH_2CH_3	86
33	n-Bu	H	H	H	280
34	n-Bu	Cl	H	H	268

TABLE VI



Prep	R_1	R_2	R	R'	M.p.(°C)
16	n-Bu	Cl	CH_3	CH_3	-
47	n-Bu	Cl	H	H	221

TABLE VII



Ex	R	R'	R_4	M.p.(°C)
72*	Pz	Pz	4-NO_2	194
83	CH_3	n-Pent	6-Cl	-
87	CH_3	n-Pent	6-CH_3	-
117	t-Bu	CH_3	4-NO_2	-
133	t-Bu	n-Pent	4-NO_2	-
180	AAE	AAE	4-NO_2	158
183	Y-t-Bu	Y-t-Bu	4-NO_2	83
195	H	CH_3	4-NO_2	234
197	H	n-Pent	4-NO_2	161
223	H	n-Pent	6-CH_3	153

Note : * 3 HCl

The products according to the invention are inhibitors of the effects of angiotensin II.

The activity of the compounds according to the invention as angiotensin II vascular receptor antagonists was evaluated by their efficacy in antagonizing the contractile response induced by angiotensin II in isolated rabbit aorta rings. The rings are suspended in a bath of Krebs-Henseleit maintained at 37°C and aerated with an O_2/CO_2 mixture (95/5; v/v), and are then stretched to a rest tension of 2 g. After one hour at rest, a contraction is caused with angiotensin II ($3 \cdot 10^{-9}$ M) in the presence of the test product preincubated for 15 minutes. The concentration (expressed in nanomol) of test product which produces a 50% inhibition of the contractile response (IC_{50}) is calculated from the concentration-response curve. The results obtained with a number of compounds according to the invention are collated in Table VIII.

The products according to the invention are useful in therapeutics in the treatment or prevention of arterial hypertension, glaucoma, circulatory disorders, restenosis due to angioplasty, developments of atheromatous or fibrinoproliferative lesions, nephropathy and retinopathy of diabetic origin, infarctus and angor and for improvement of the cognitive function.

According to the invention, a therapeutic composition is recommended which contains at least one compound of formula I or one of its addition salts in a therapeutically effective amount in association with a physiologically acceptable excipient.

It is also recommended to use the compounds of formula I or one of their addition salts as angiotensin II antagonists in order to obtain a drug for the prevention or cure of arterial hypertension, circulatory disorders and glaucoma.

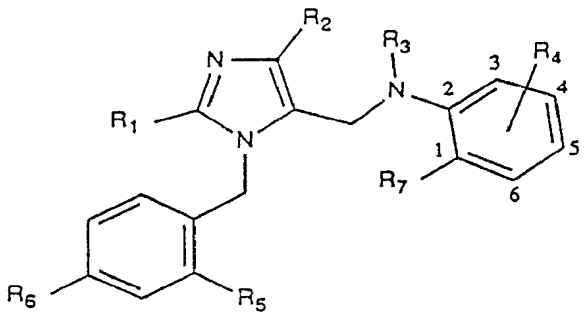
TABLE VIII

Ex	IC_{50} (x10^{-9} M)	Ex	IC_{50} (x10^{-9} M)
26	100	156	82
28	80	157	54
32	3.6	158	75
33	7.1	161	64
34	8.4	163	50
35	1.2	164	40
36	7	166	15
39	106.2	168	67
40	57.6	170	80
41	5.1	174	80
42	5.1	178	67
43	6.3	180	30
44	5.3	181	80
45	6.7	183	60
46	10.5	187	7
47	71.3	195	82
48	5.3	197	55
49	13.2	198	4.6
50	5.7	201	10
51	10.8	202	14.7
52	40.2	203	4.4
55	69.1	204	9.5
66	8.8	205	5.5
67	1.5	209	70
68	30	210	84
76	90	211	0.8
134	35	212	46
141	10	226	6
145	40	228	2
148	12		
149	5		
155	8.7		

The embodiments of the invention, in which an exclusive property or privilege is claimed are defined as follows:

1. A phenylaminomethylimidazole compound which is selected from the group consisting of:

(i) the phenylaminomethylimidazoles of the formula



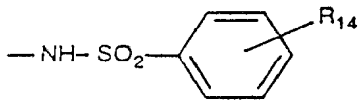
(I)

in which:

- R_1 is a C_1-C_4-alkyl group;
- R_2 is the hydrogen atom, a halogen, a C_1-C_4-alkylthio group or a C_1-C_3-perfluoroalkyl group;
- R_3 is the hydrogen atom, a C_1-C_4-alkyl group or a group COR_8, in which R_8 is a C_1-C_4-alkyl group;
- R_4 is in the 3-, 4-, 5- or 6-position and is the hydrogen atom, one or more C_1-C_4-alkyl, C_1-C_4-alkoxy, azido or nitro groups or one or more halogens, or forms a 2-aminonaphthyl group with the aminophenyl group to which it is bonded;
- R_5 is a hydrogen atom or a halogen; and
- R_6 and R_7, which are identical or different, are each a tetrazol-5-yl group or a group COR_9, in which R_9 is:
  - a hydroxyl group,
  - a C_1-C_{16}-alkoxy group,
  - a cyclopropylmethoxy group,
  - a phenoxy group,
  - a benzyloxy group,
  - a 2-phenylethoxy group,

- a glyceryl group,
- an isopropylideneglyceryl group,
- a 2-methoxyethoxy group,
- a 2-oxobutoxy group,
- a 1-methyl-2-oxobutoxy group,
- a 2-(N,N-diethylamino)ethoxy group,
- a morpholinoethoxy group,
- an N-(ethoxy)nicotinamide group,
- a group $O-CHR_{15}-O(CO)-R_{12}$, in which R_{15} is the hydrogen atom or a C_1-C_3-alkyl group and R_{12} is a C_1-C_7-alkyl group, a cyclopentyl group, a cyclohexyl group, a cyclopentylmethyl group or a cyclohexylmethyl group,
- an oxyacetate group of the formula $O-CHR_{17}-CO_2-R_{16}$, in which R_{16} and R_{17} are each independently the hydrogen atom or a C_1-C_5-alkyl group,
- an oxyacetamide group of the formula $O-CH_2-CO-NR_{10}R_{11}$, in which R_{10} and R_{11}, which are identical or different, are each a C_1-C_4-alkyl group or a hydroxyethyl group or form a 4-methylpiperazin-1-yl group with the nitrogen atom to which they are bonded, or
- an amino group of the formula $-NR_{18}R_{19}$, in which R_{18} and R_{19} are each independently the hydrogen atom, a C_1-C_4-alkyl group, a methoxy group or a 2-(N,N-dimethylamino)propyl group, or $-NR_{18}R_{19}$ is an amino acid residue of the glycine or valine structure in which the acid group is optionally protected in the form of an ester or amide;

- it also being possible for R_6 to be:
- a group COR_{13}, in which R_{13} is a methylsulfonylamino group of the formula $-NH-SO_2-CH_3$ or an arylsulfonylamino group of the formula



in which R_{14} is the hydrogen atom, a halogen, an azido group, a C_1-C_4-alkyl group or a methoxy group and can be located in the ortho-, meta- or para-position; and

- it being possible for R_5 and R_7 taken together to form, with the nitrogen atom and the phenyl group to which they are respectively bonded, a 2-carboxyindol-1-yl or 2-ethoxycarbonylindol-1-yl ortho-fused nitrogen-containing heterocycle; and

(ii) the addition salts of the compounds of formula I with mineral and organic acids or with mineral and organic bases.

2. A compound according to claim 1 wherein, in formula I, R_6 or R_7 is a group COOH.

3. A compound according to claim 2 wherein the carboxyl groups R_6 and R_7 are salified with an organic or mineral base.

4. A compound of formula I according to claim 1 which is salified with an organic or mineral acid.

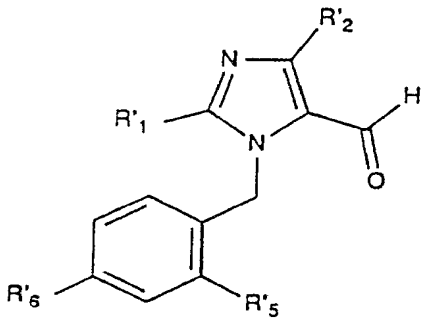
5. A compound according to claim 1 wherein, in formula I, R_6 or R_7 is a methylsulfonylaminocarbonyl group or an arylsulfonylaminocarbonyl group.

6. A therapeutic composition which contains at least one compound of formula I or one of its addition salts in a therapeutically effective amount in association with a physiologically acceptable excipient.

7. Use of a compound according to claim 1 as an angiotensin II antagonist in order to obtain a drug for the prevention or cure of arterial hypertension, circulatory disorders or glaucoma.

8. An intermediate useful in the synthesis of compounds of formula I according to claim 1, which is a 1-

phenylmethylimidazole-5-carboxaldehyde product of the formula

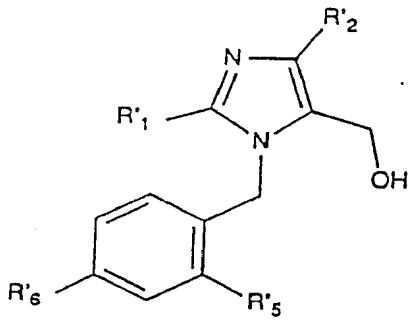


in which:

(i) R'_1 is an n-propyl group, R'_2 is a hydrogen atom or a halogen, R'_5 is the hydrogen atom and R'_6 is a cyano group or a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group or a benzyloxy group, or

(ii) R'_1 is an n-butyl group, R'_2 and R'_5 are the hydrogen atom and R'_6 is a group COR'_9 in which R'_9 is a t-butoxy or benzyloxy group.

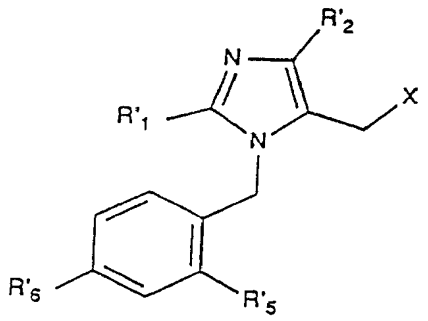
9. An intermediate useful in the synthesis of compounds of formula I according to claim 1, which is a 1-phenylmethyl-5-hydroxymethylimidazole product of the formula



in which:

R'_1 is a C_1-C_4-alkyl group, R'_2 is the hydrogen atom or a halogen, R'_5 is the hydrogen atom and R'_6 is a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group or a benzyloxy group.

10. An intermediate useful in the synthesis of compounds of formula I according to claim 1, which is a 1-phenylmethyl-5-halogenomethylimidazole product of the formula

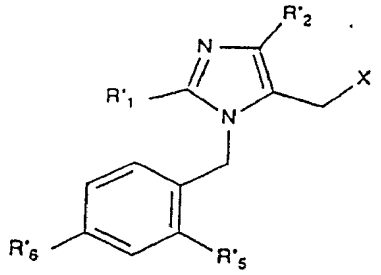


in which:

R'_1 is an n-butyl group, R'_2 and R'_5 are the hydrogen atom, R'_6 is a group COR'_9 in which R'_9 is a t-butoxy or benzyloxy group, and X is a halogen.

11. A method of preparing a compound according to claim 1, which comprises the steps consisting in:

(a) subjecting a compound of the formula

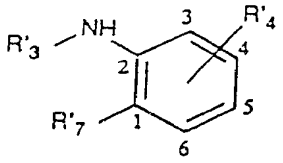


(II')

in which:

- R'_1 is a C_1-C_4-alkyl group;
- R'_2 is the hydrogen atom, a halogen, a C_1-C_4-alkylthio group or a C_1-C_3-perfluoroalkyl group;
- R'_5 is a hydrogen atom or a halogen;
- R'_6 is a cyano group or a group COR'_9, in which R'_9 is a C_1-C_{16}-alkoxy group, a benzyloxy group or an isopropylideneglyceryl group; and
- X is a halogen, especially the chlorine atom, or a paratoluenesulfonyl group,

to nucleophilic substitution by reaction with a compound of the formula



(III')

in which:

- R'_3 is the hydrogen atom or a C_1-C_4-alkyl group;
- R'_4 is in the 3-, 4-, 5- or 6-position and is the hydrogen atom, one or more C_1-C_4-alkyl, C_1-C_4-alkoxy, azido or nitro groups or one or more halogens, or forms a 2-aminonaphthyl group with the aminophenyl group to which it is bonded; and
- R'_7 is a cyano group or a group COR'_9, in which R'_9 is:

  - a C_1-C_{16}-alkoxy group, a benzyloxy group, an isopropylideneglyceryl group, a phenoxy group, a 2-phenylethoxy group, a 2-methoxyethoxy group, a 2-oxobutoxy group, a 1-methyl-2-oxobutoxy group or a 2-(N,N-diethylamino)ethoxy group,

  - a group $O-CHR_{15}-O(CO)-R_{12}$, in which R_{15} is the hydrogen atom or a C_1-C_3-alkyl group and R_{12} is a C_1-C_7-alkyl group, a cyclopentyl group, a cyclohexyl

group, a cyclopentylmethyl group or a cyclohexylmethyl group,

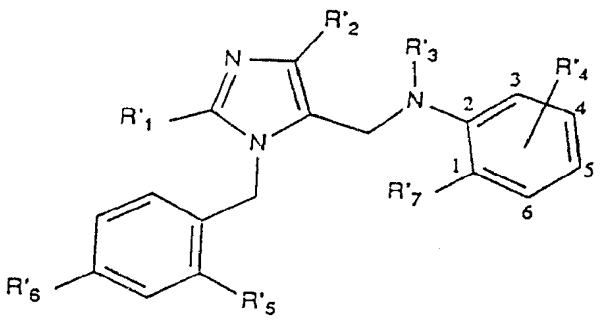
- an oxyacetate group of the formula $O-CHR_{17}-CO_2-R_{16}$, in which R_{16} and R_{17} are each independently the hydrogen atom or a C_1-C_5-alkyl group,

- an oxyacetamide group of the formula $O-CH_2-CO-NR_{10}R_{11}$, in which R_{10} and R_{11}, which are identical or different, are each a C_1-C_4-alkyl group or a hydroxyethyl group, or

- an amino group of the formula $-NR_{18}R_{19}$, in which R_{18} and R_{19} are each independently the hydrogen atom, a C_1-C_4-alkyl group, a methoxy group or a 2-(N,N-dimethylamino)propyl group, or $-NR_{18}R_{19}$ is an amino acid residue of the glycine or valine structure in which the acid group is optionally protected in the form of an ester or amide;

- it being possible for R'_3 and R'_7 taken together to form, with the nitrogen atom and the phenyl group to which they are respectively bonded, a 2-carboxyindol-1-yl or 2-ethoxycarbonylindol-1-yl ortho-fused nitrogen-containing heterocycle,

in an anhydrous medium, in the presence or absence of a polar or non-polar and aprotic solvent, for example toluene, xylenes, tetrahydrofuran, dimethylformamide, chlorinated hydrocarbons, ethers, dioxane, N-methylpyrrolidin-2-one, N,N'-dimethylpropyleneurea or dimethyl sulfoxide, and in the presence or absence of a strong base, for example triethylamine, 2,6-lutidine, sodium or potassium hydride, potassium or lithium hexamethyldisilylamide or lithium diisopropylamide, at a rate of 1 mol of compound II' to 1 to 20 mol of compound III', at a temperature between room temperature (15-25°C) and about 200°C, for 0.1 to 12 hours, to give a compound of the formula



(I')

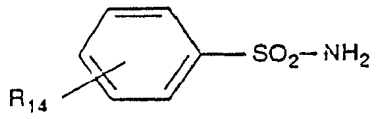
in which R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 are defined as indicated above; and

(b) if necessary, subjecting the resulting compound of formula I' to the following treatments:

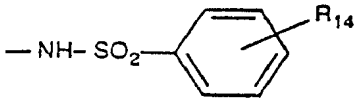
(i) saponification of a compound of formula I' in which at least one of the groups R'_6 and R'_7 is a group COR'_9 in which R'_9 is a C_1-C_{16}-alkoxy group by the methods known to those skilled in the art, especially in the presence of a strong base, for example an aqueous solution of sodium or potassium hydroxide, in dimethoxyethane or an alcohol such as methanol, to give a compound of formula I in which R_6 and R_7 are a group COOH or R_6 is a group COOH and R_7 is a group COR_9 in which R_9 is a C_1-C_{16}-alkoxy group;

(ii) esterification of the compound thus obtained in stage (i) by the methods known to those skilled in the art, especially by reaction with an appropriate alcohol or by reaction with an appropriate halogenated derivative, to give a compound of formula I in which R_6 and R_7 are a group COR_9 in which R_9 is as defined for the groups R'_9 indicated above;

(iii) acylation of methylsulfonamide or an arylsulfonamide of the formula



in which R_{14} is the hydrogen atom, a halogen, an azido group, a C_1-C_4-alkyl group or a methoxy group, with a monoacid obtained in stage (i) by the methods known to those skilled in the art, especially in the presence of a coupling reagent, for example 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride or N,N-di-cyclohexylcarbodiimide, to give a compound of formula I in which R_6 is a group COR_{13} in which R_{13} is a methyl-sulfonylamino group of the formula $-NH-SO_2-CH_3$ or an arylsulfonylamino group of the formula



in which R_{14} is defined as indicated above, R_7 is a group COR_9 in which R_9 is a C_1-C_{16}-alkoxy group, and R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for R'_1, R'_2, R'_3, R'_4 and R'_5 respectively;

(iv) acylation of a compound of formula I' in which R'_3 is the hydrogen atom and R'_1, R'_2, R'_4, R'_5, R'_6 and R'_7 are defined as indicated above by the methods known to those skilled in the art, especially by reaction with an acid anhydride, for example acetic anhydride, to give a compound of formula I in which R_3 is a group COR_8 in which R_8 is a C_1-C_4 alkyl group, and R_1, R_2, R_4, R_5, R_6 and R_7 are defined as indicated above for R'_1, R'_2, R'_4, R'_5, R'_6 and R'_7 respectively;

(v) if necessary, deprotection of a compound of formula I' in which at least one of the groups R'_6 and R'_7 is a group COR'_9 in which R'_9 is a C_1-C_4-alkoxy group, a

benzyloxy group or an isopropylideneglyceryl group by the methods known to those skilled in the art, especially by treatment in an acid medium or by catalytic hydrogenation, to give a compound of formula I in which at least one of the groups R_6 or R_7 is a group COOH or CO-glyceryl and the other group is a group COR_9 in which R_9 is defined as indicated above for R'_9; and

(vi) conversion of a compound of formula I' in which R'_6 or R'_7 is a cyano group to a compound of formula I in which R_6 or R_7 is a tetrazol-5-yl group by the methods known to those skilled in the art, especially by the 1,3-dipolar cycloaddition of trialkyltin or triaryltin azides.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente